Optimizing Bedaquiline for Cardiotoxicity by Structure Based Virtual Screening, DFT analysis and Molecular Dynamic Simulation Studies to Identify Selective MDR-TB Inhibitors

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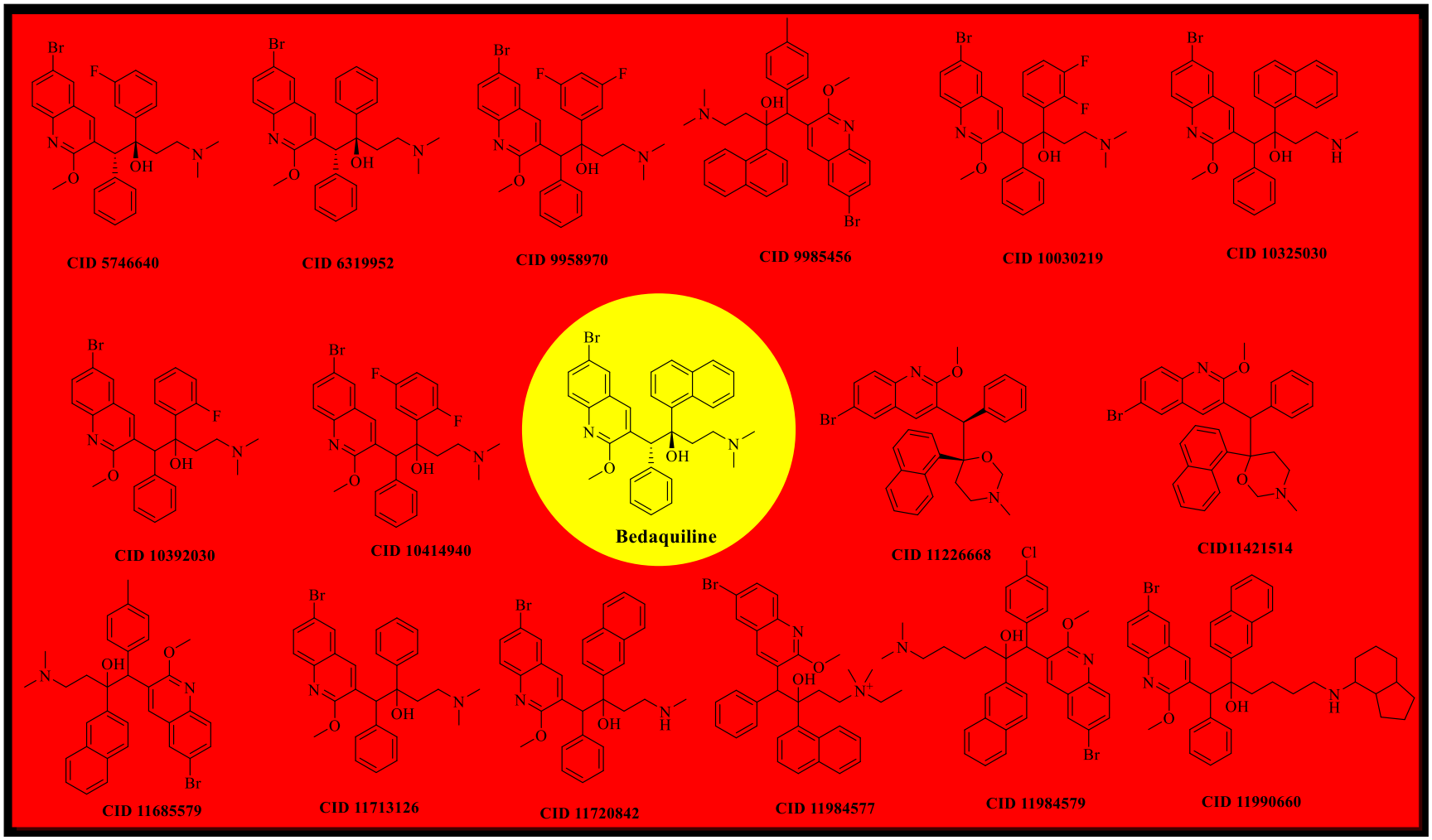
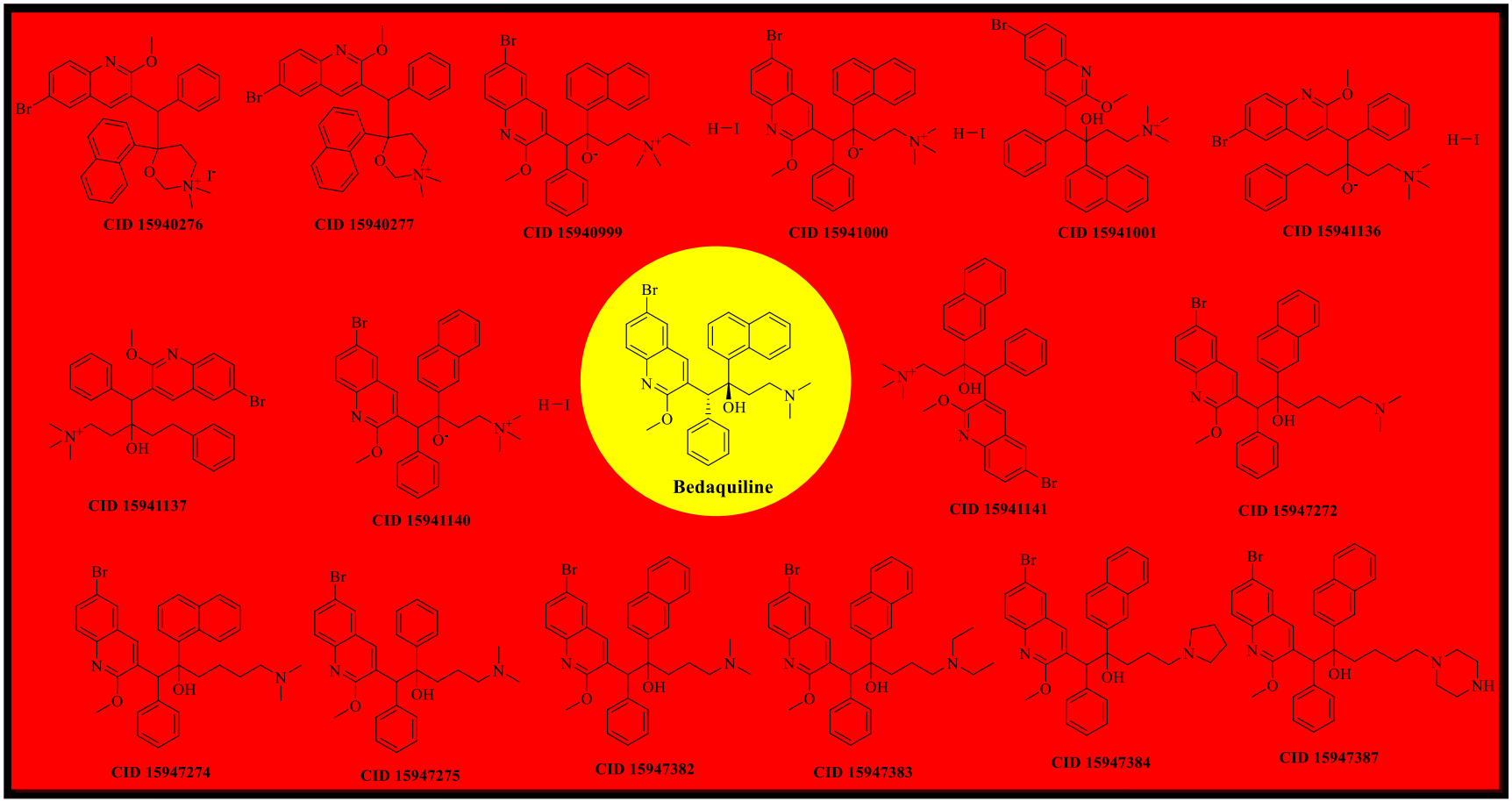


Figure S1. Library of Bedaquiline analogues obtained from Pubchem database



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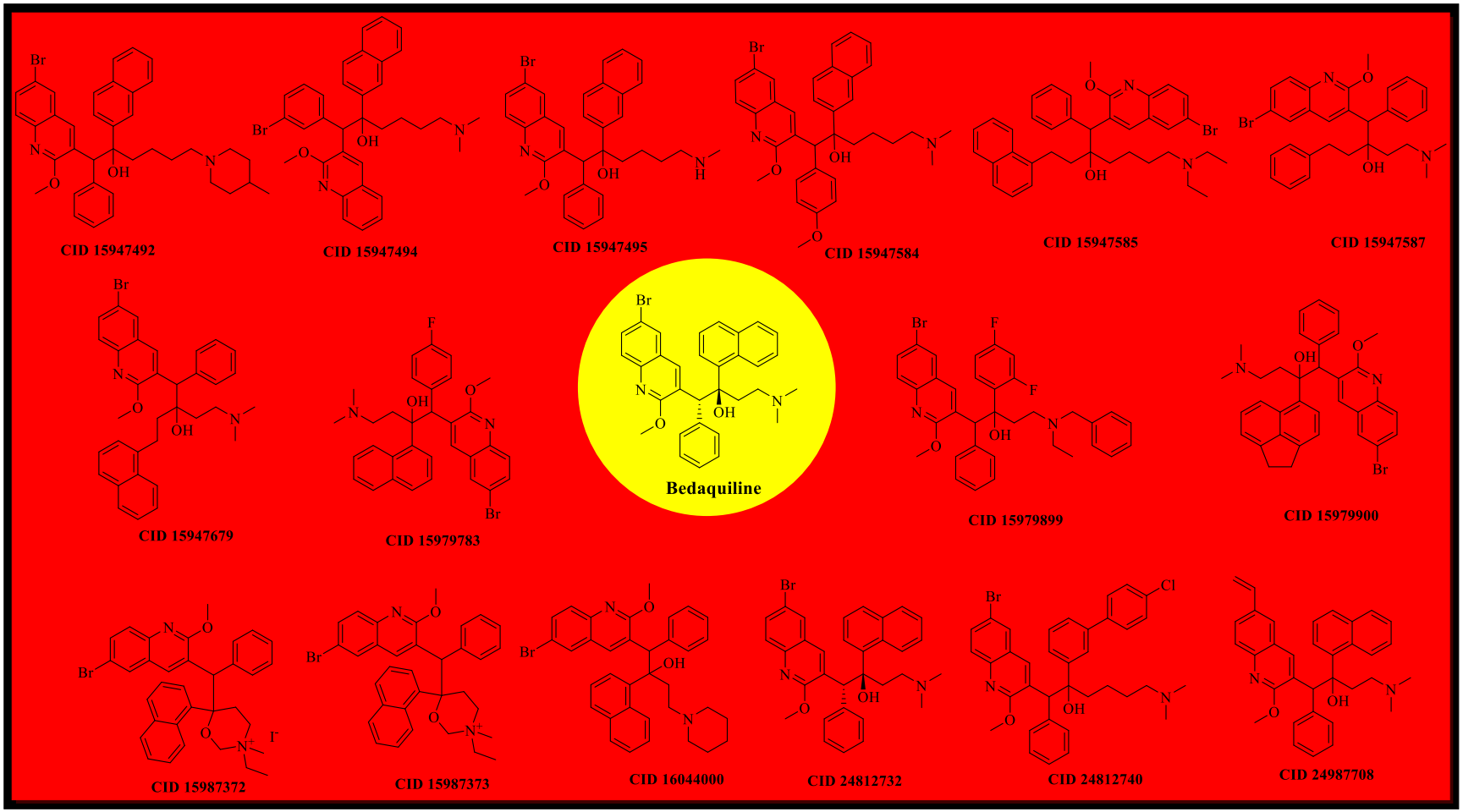


Figure S1. *Continue…*

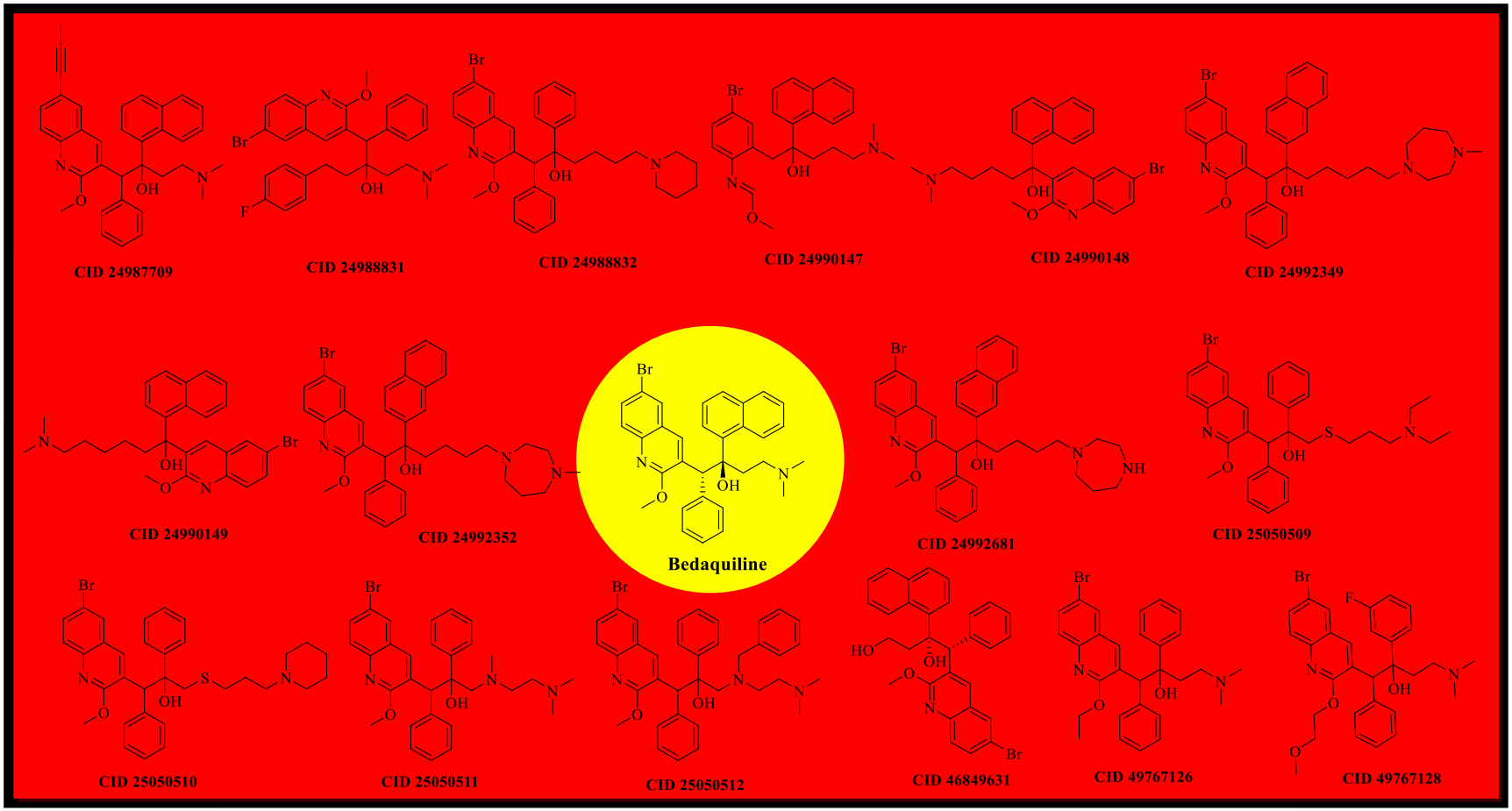


Figure S1. *Continue…*

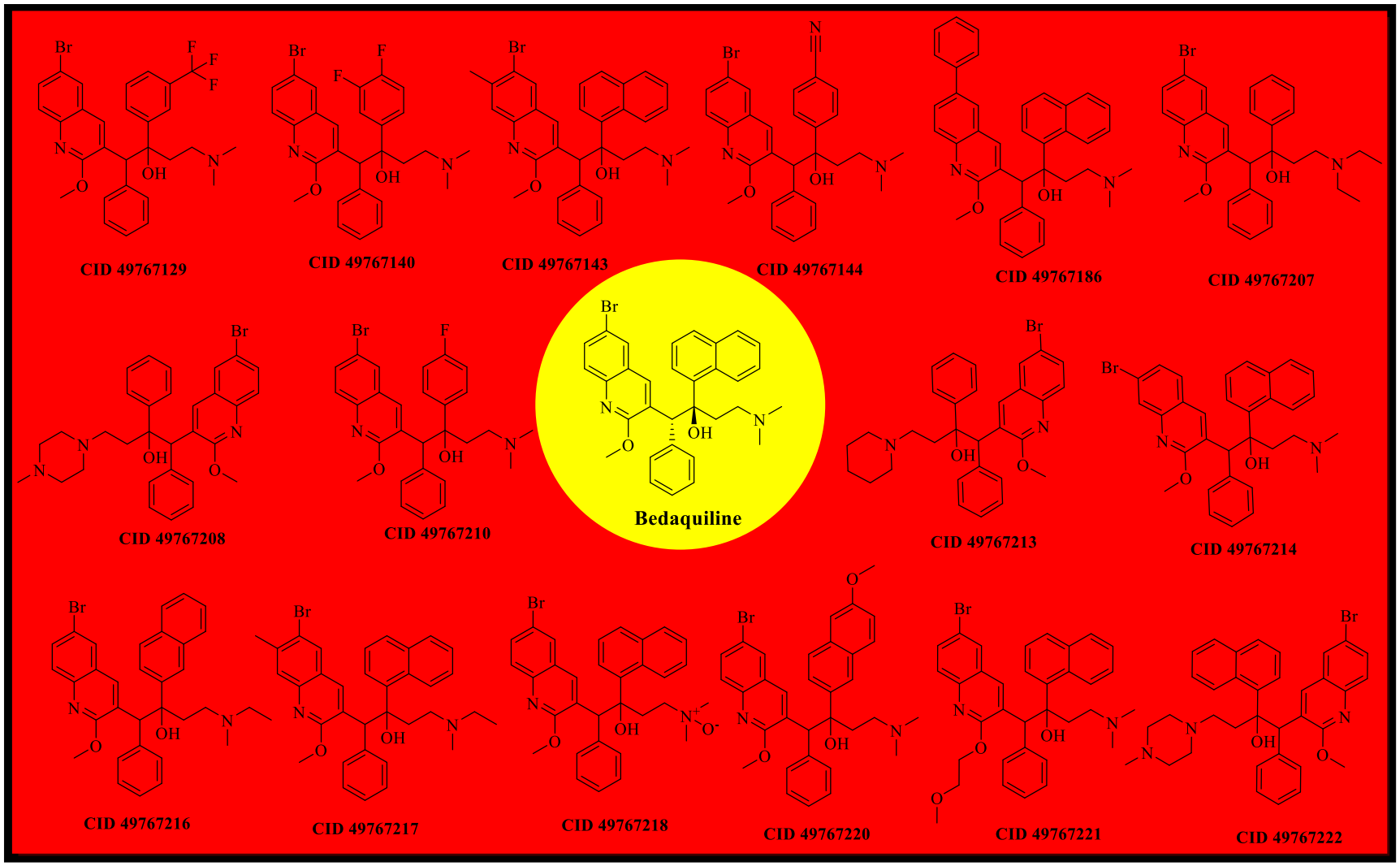
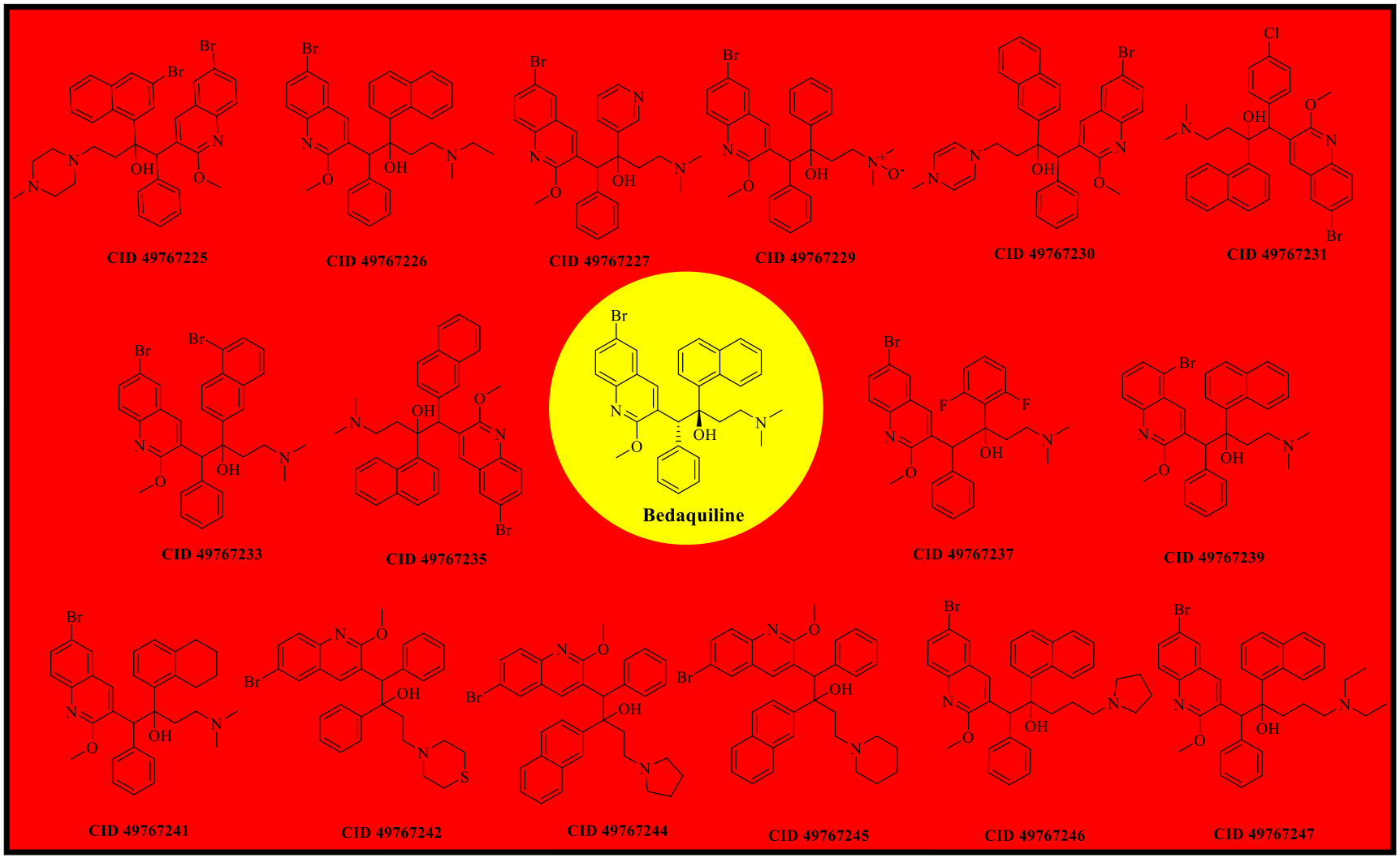


Figure S1. *Continue…*



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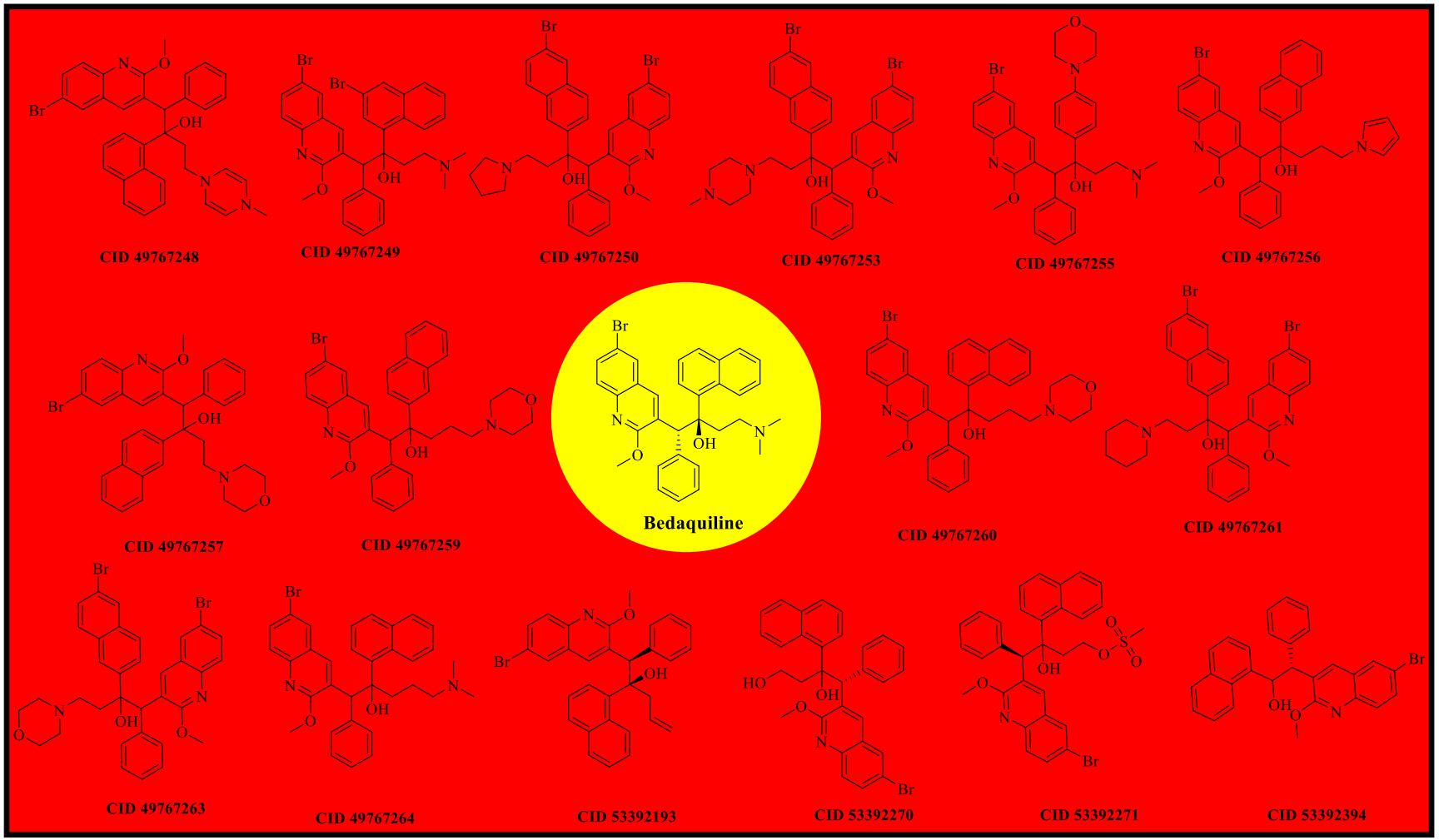


Figure S1. *Continue…*

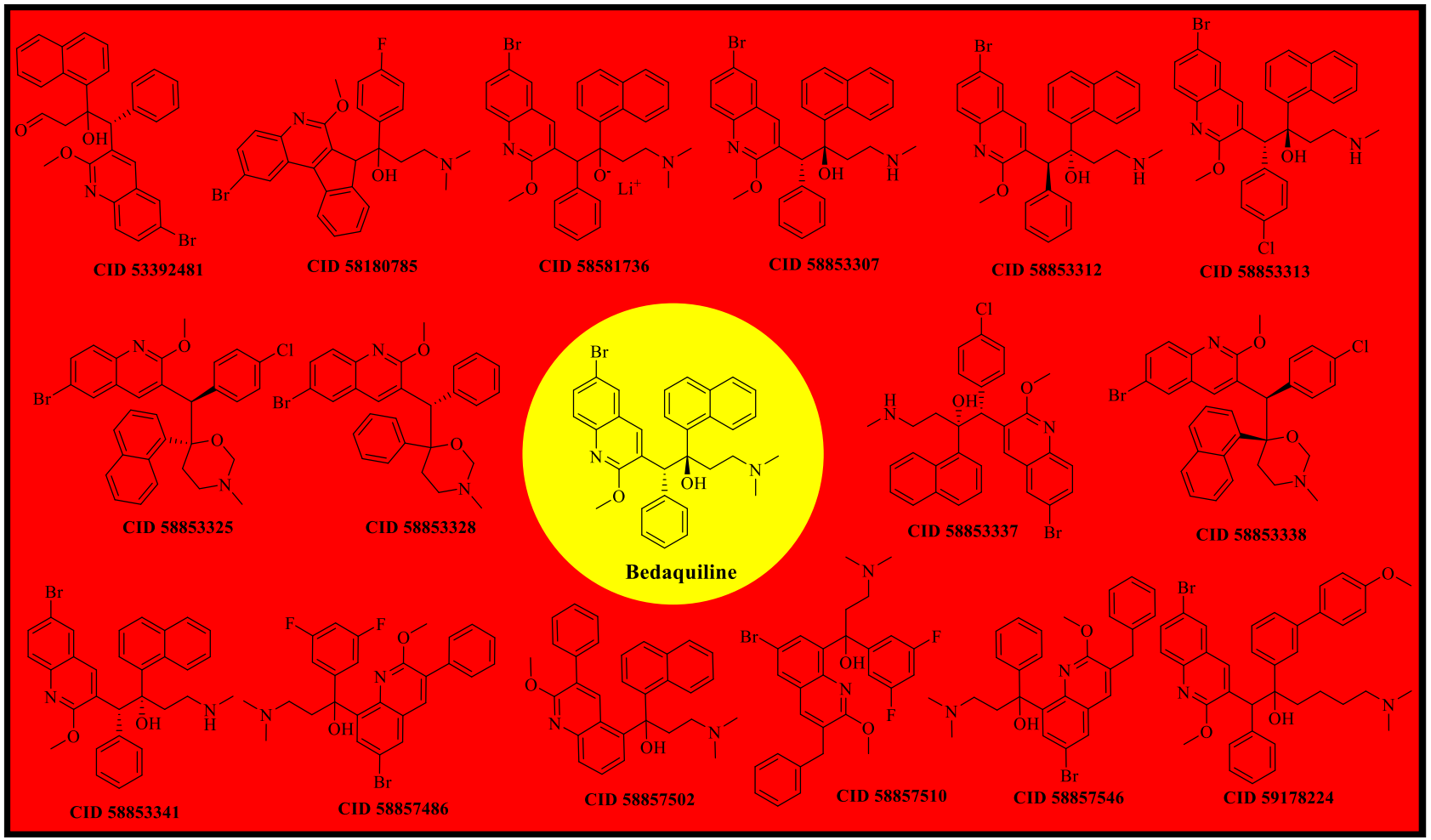


Figure S1. *Continue…*

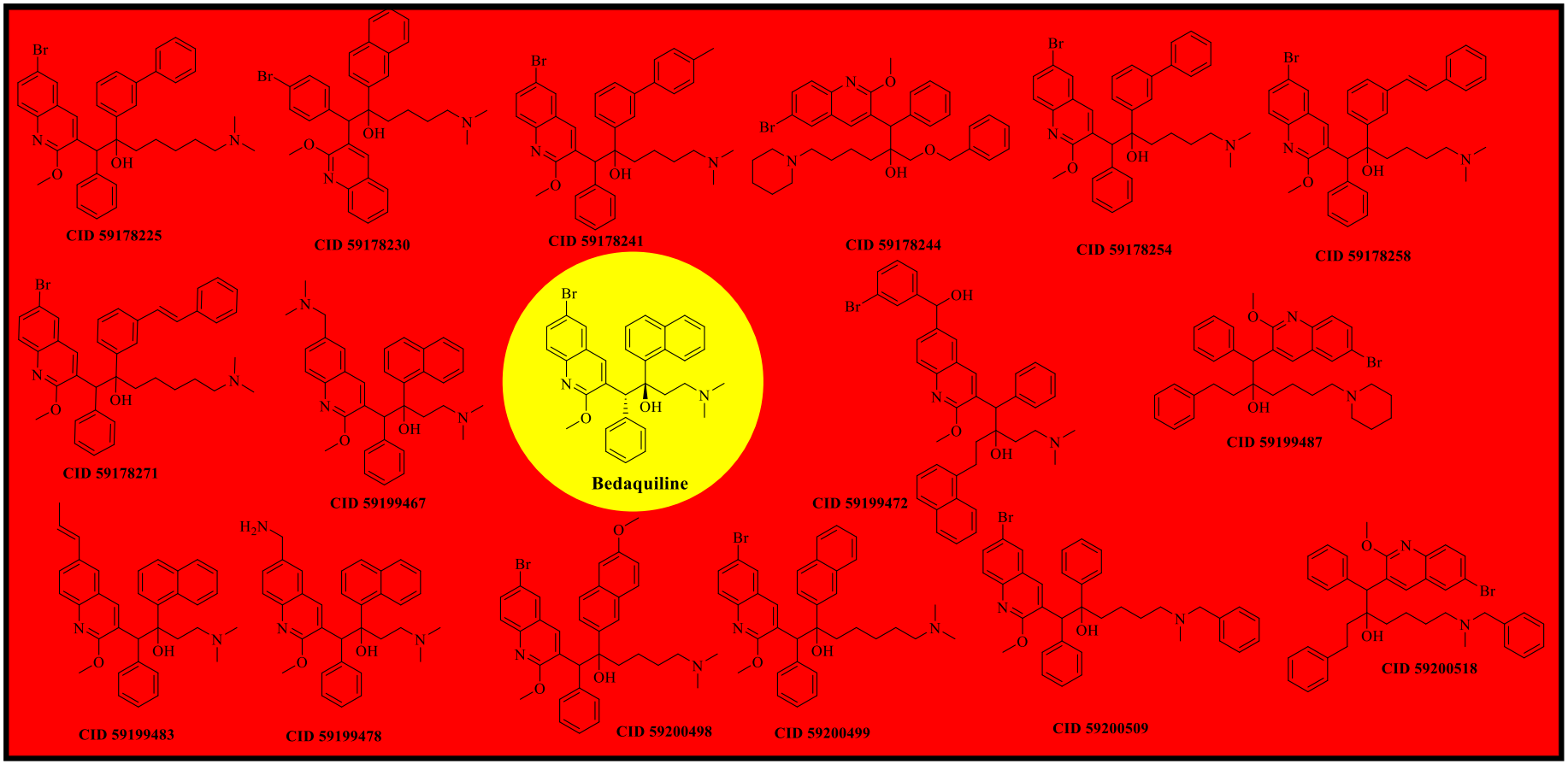
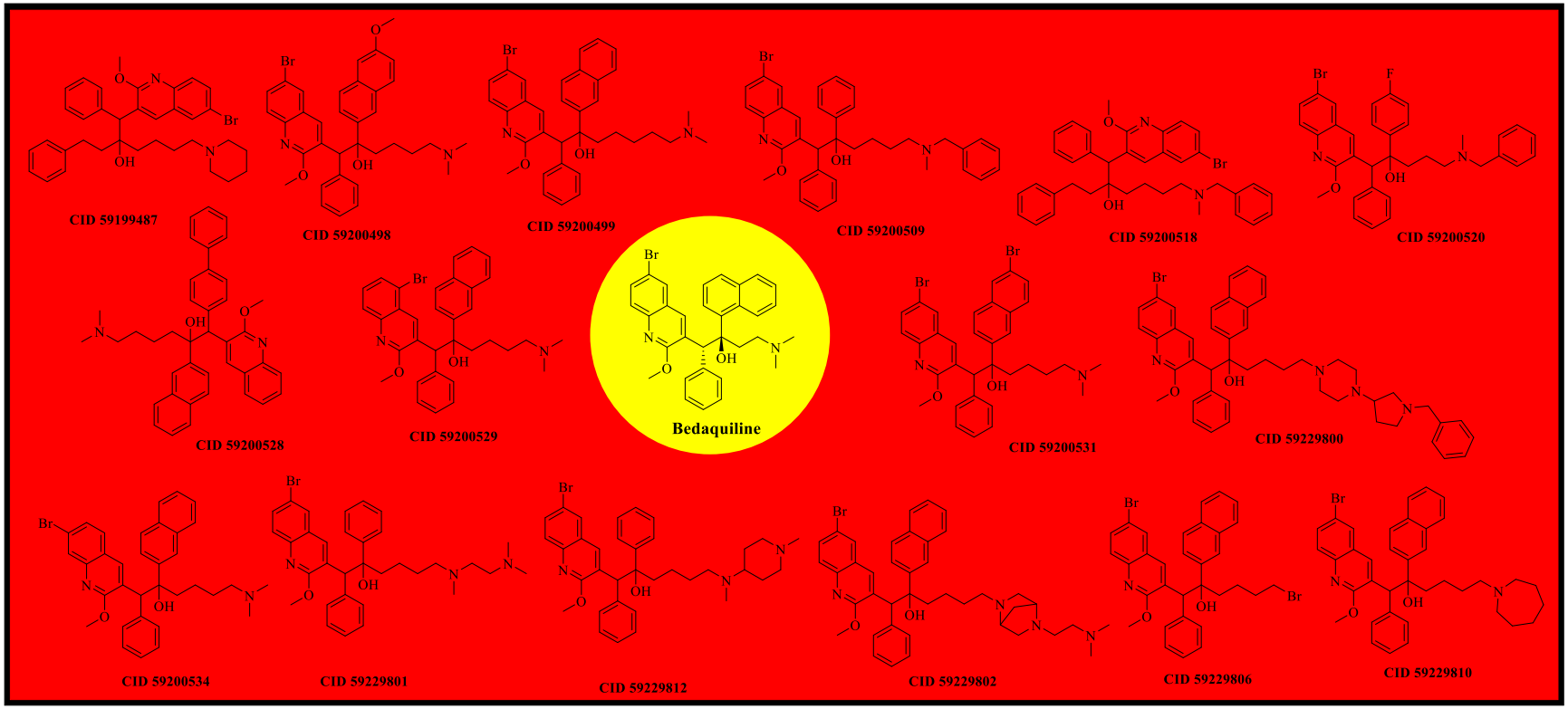


Figure S1. *Continue…*



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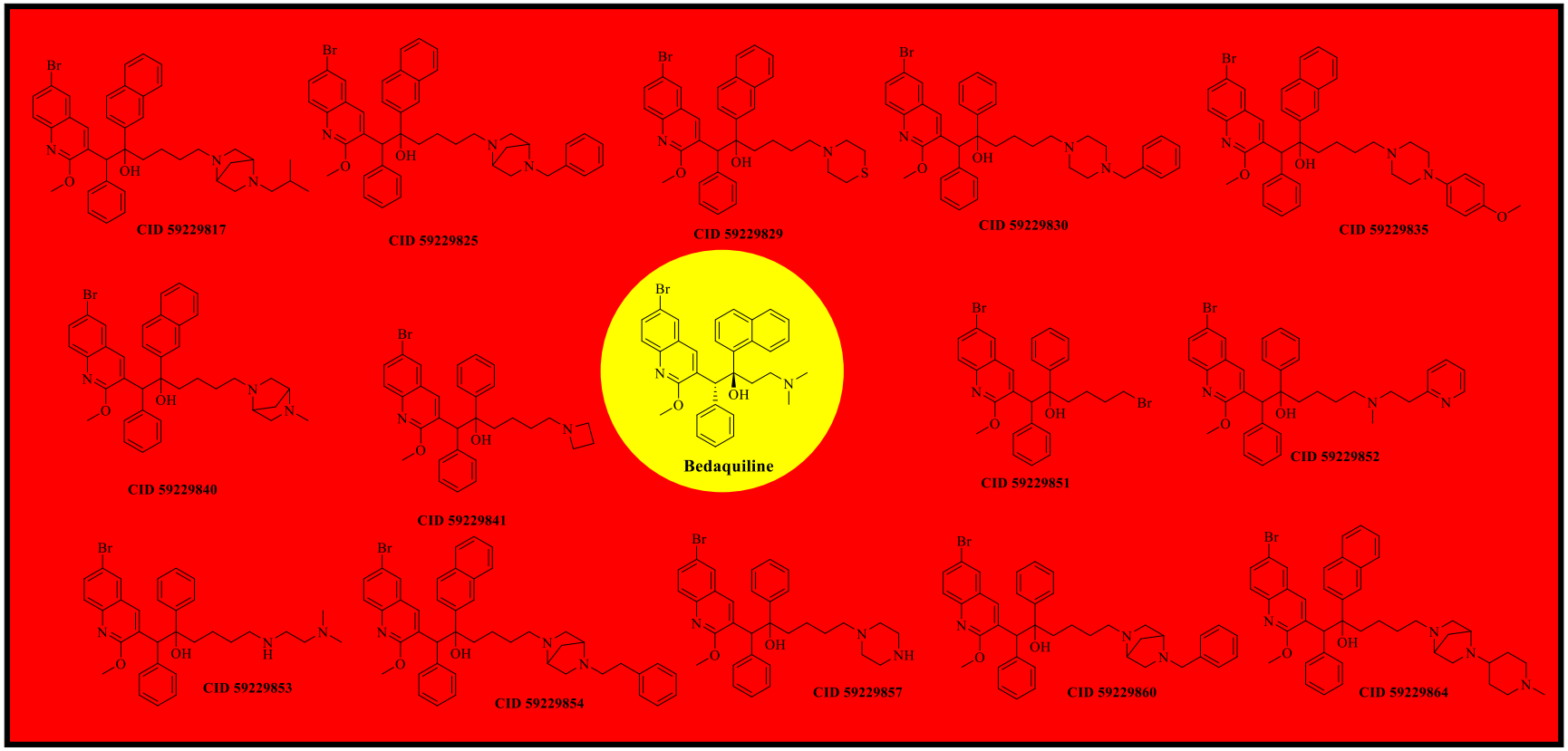


Figure S1. *Continue…*

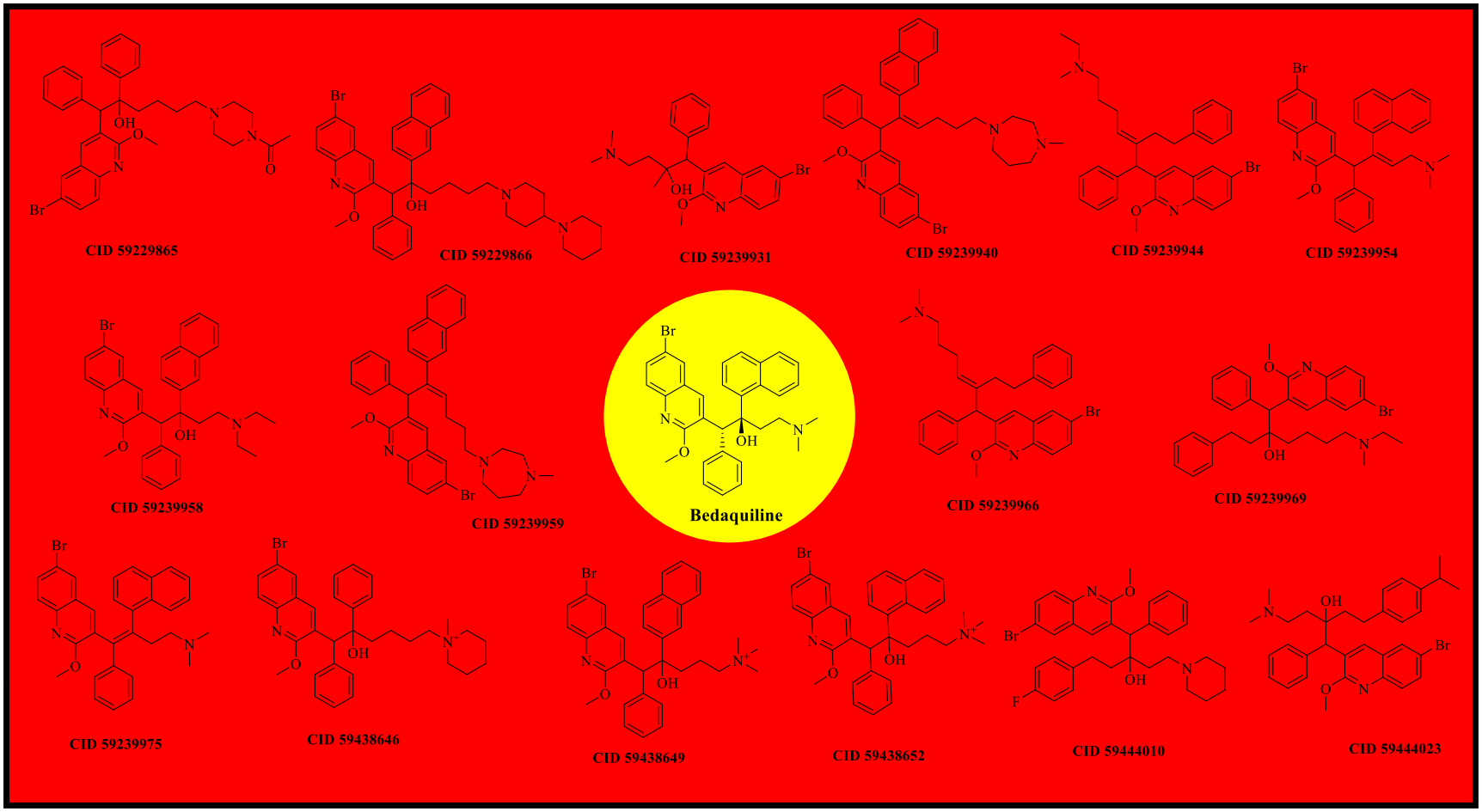


Figure S1. *Continue…*

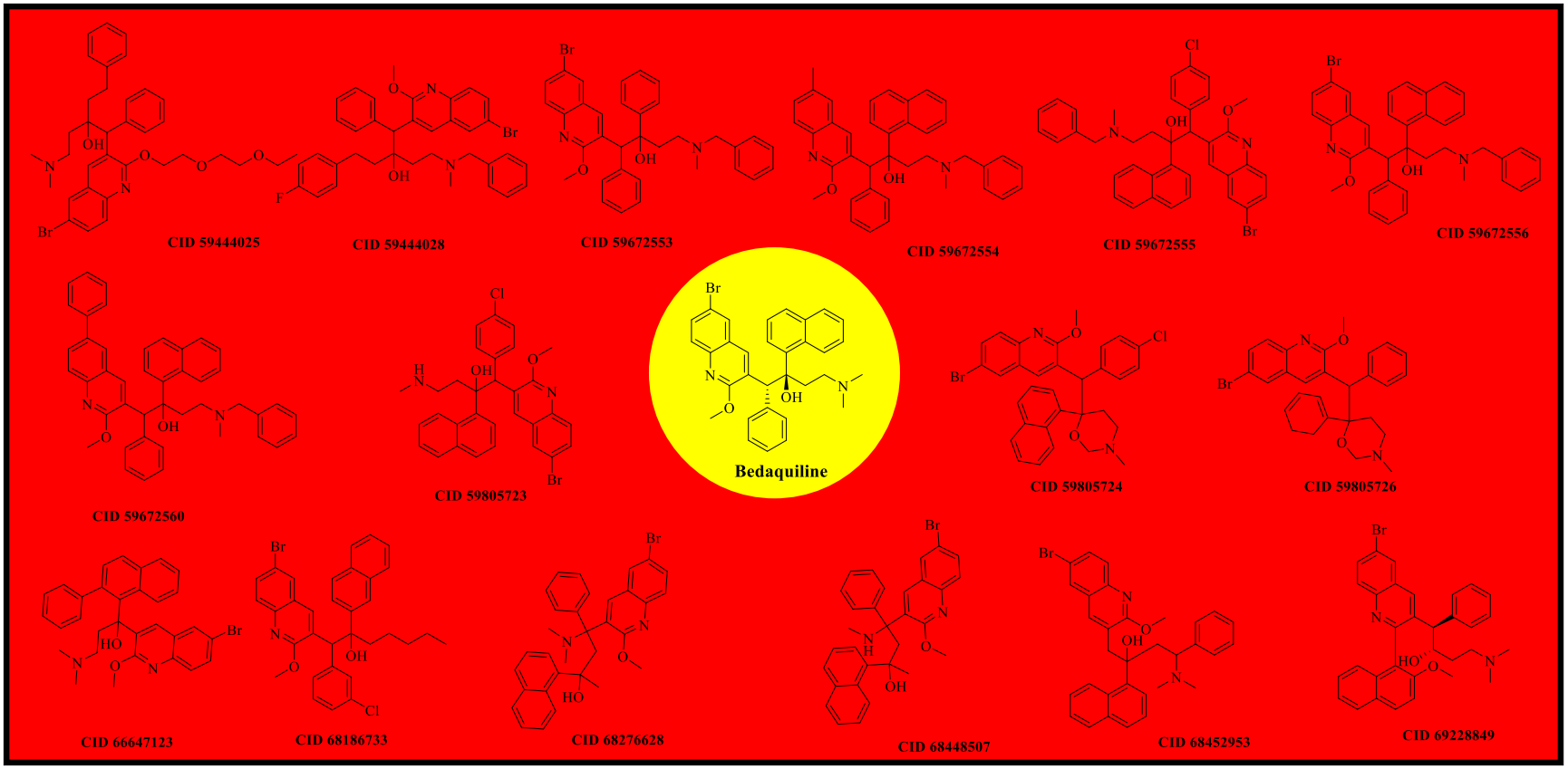


Figure S1. *Continue…*

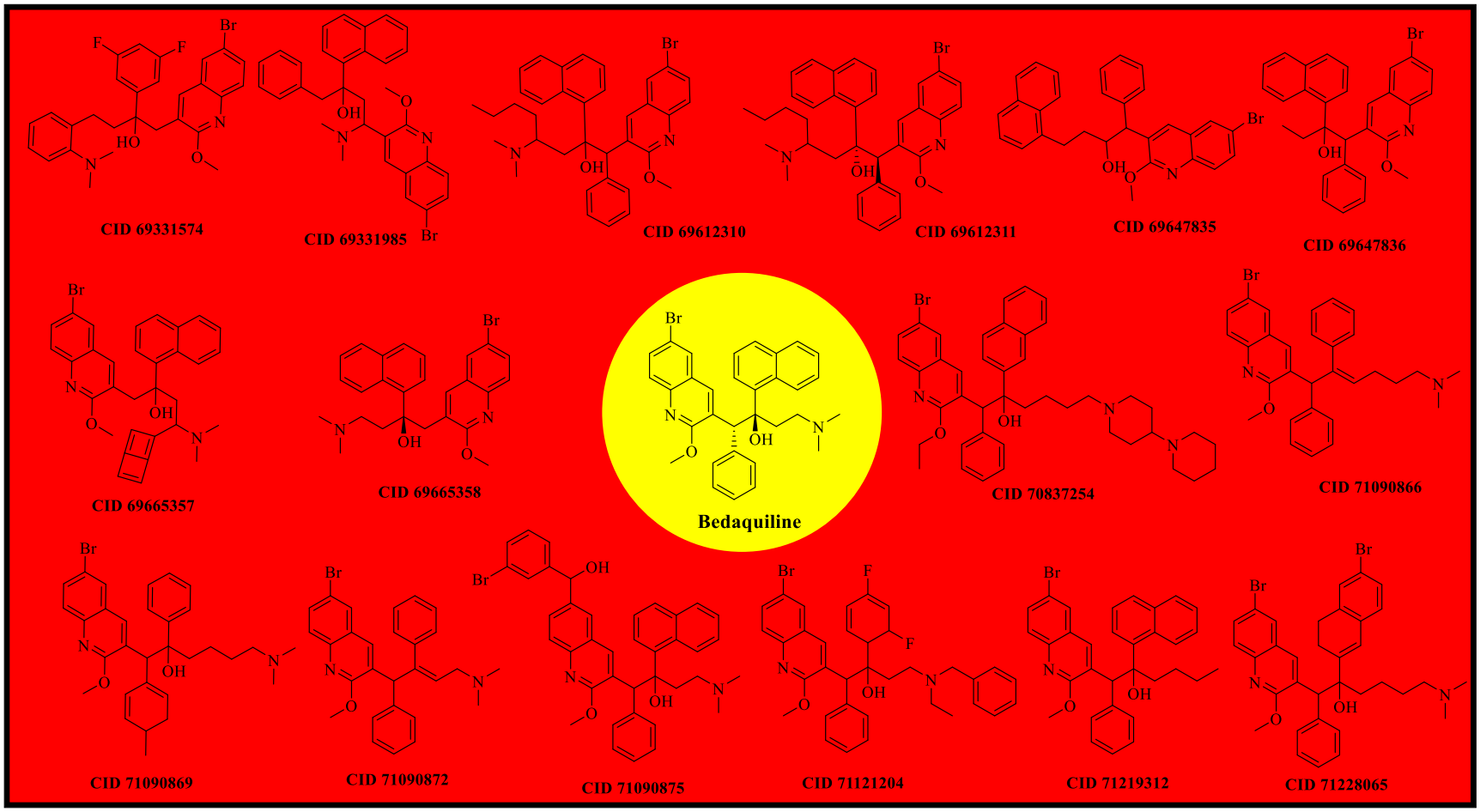


Figure S1. *Continue…*

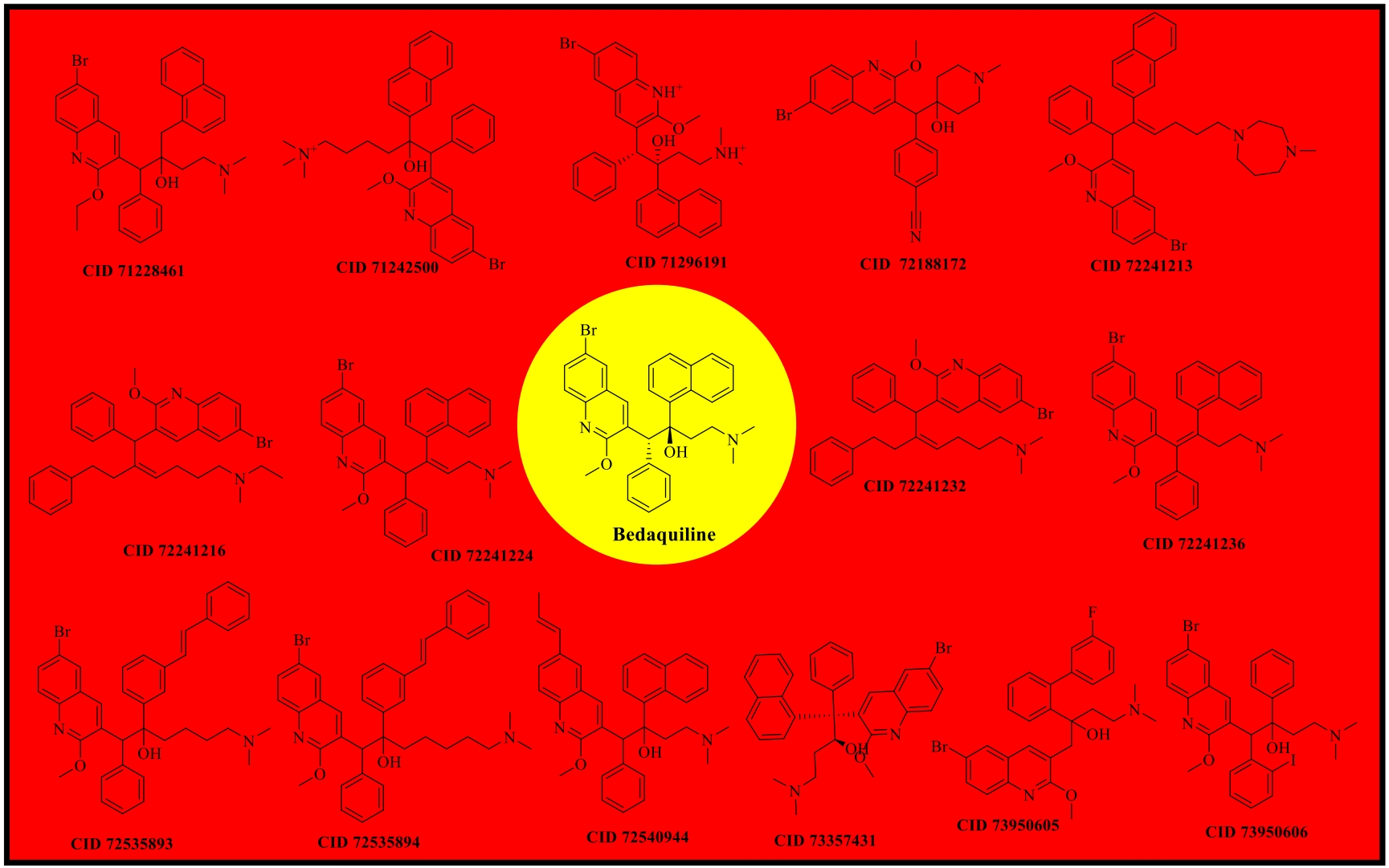


Figure S1. *Continue…*

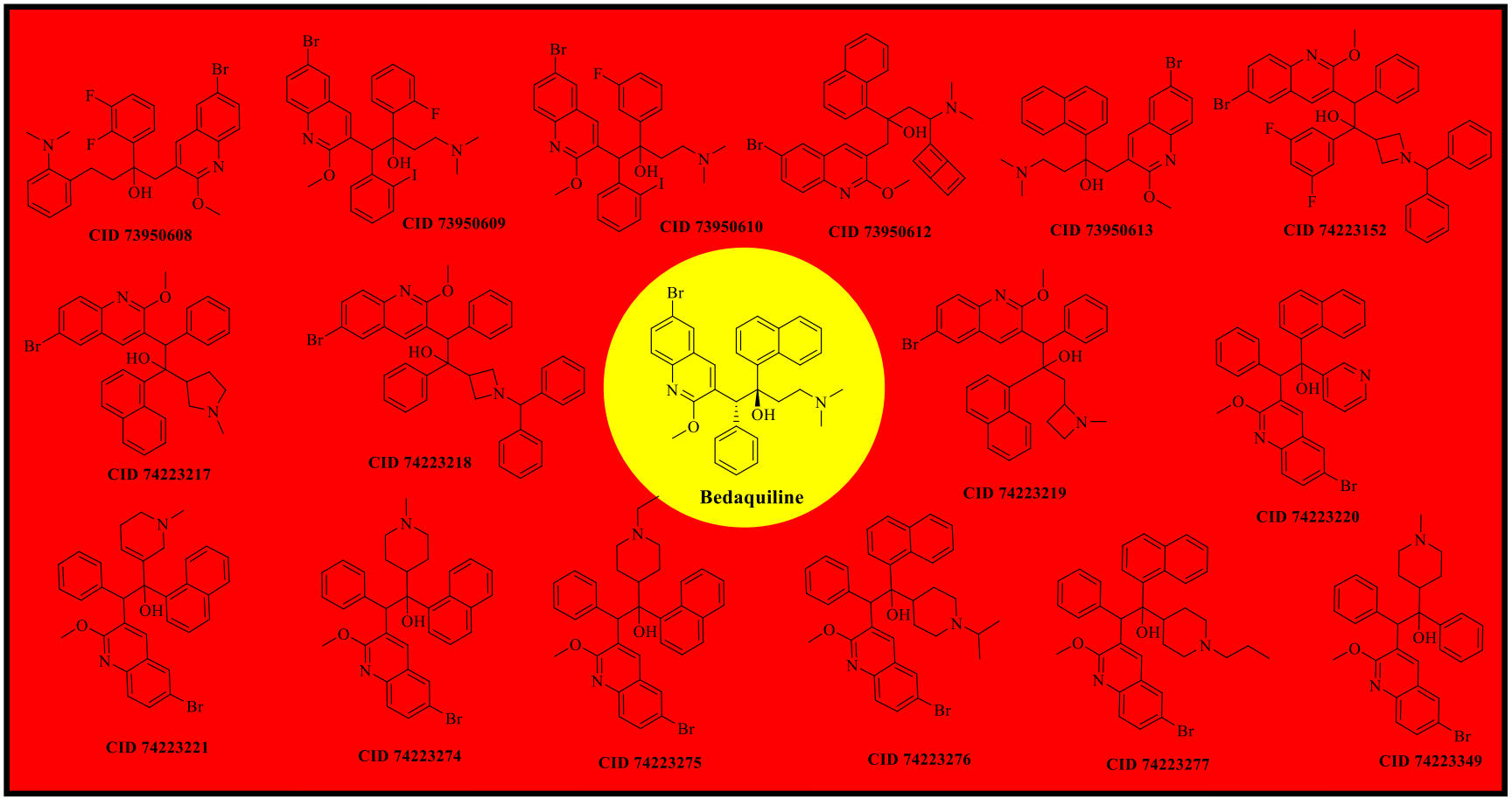


Figure S1. *Continue…*

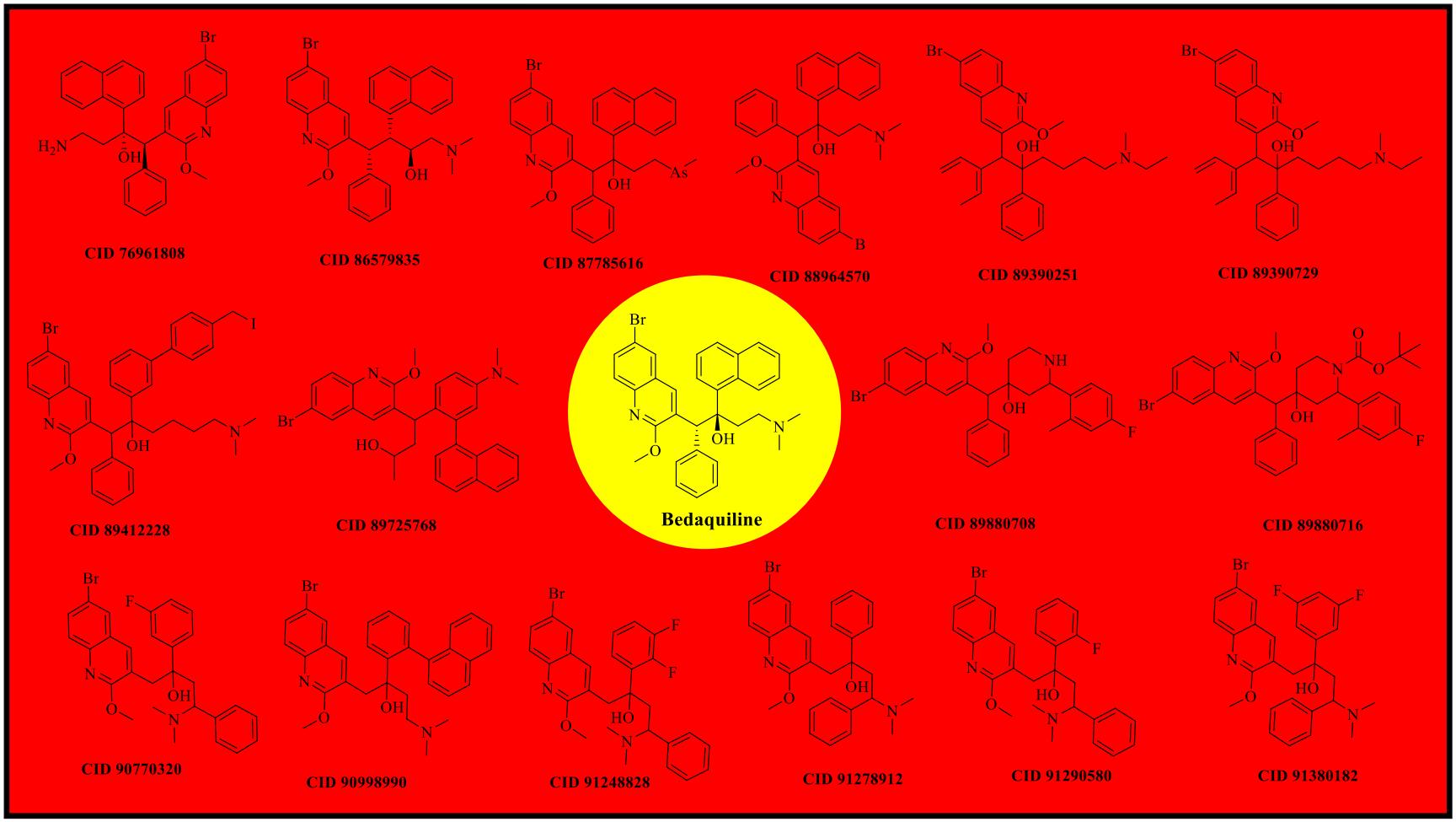


Figure S1. *Continue…*

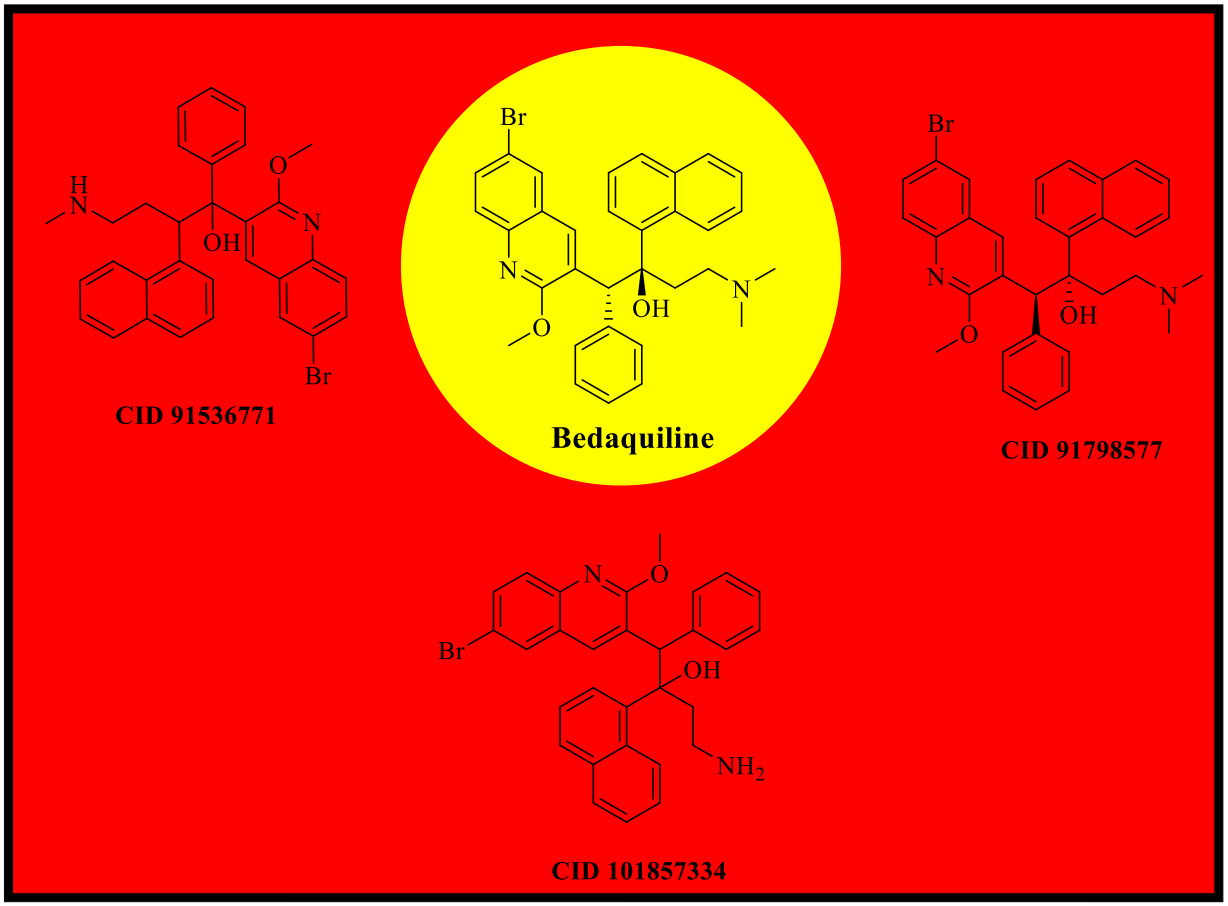


Figure S1. *Continue…*

Table S1. Bedaquiline analogues hERG inhibition (QPlogHERG) predicted by QikProp, Schrodinger 9.0.

CID Code	QPlogHERG	Source File	QPlogHERG	CID Code	QPlogHERG	CID Code	QPlogHERG
Bedaquiline	**-7.806**	74223220	-7.729	68452953	-7.543	49767241	-7.258
15979899	-7.799	10325030	-7.727	49767126	-7.539	73950610	-7.258
68276628	-7.799	15947274	-7.727	59200520	-7.538	74223219	-7.25
66647123	-7.795	59672553	-7.727	49767218	-7.537	49767260	-7.247
24988831	-7.794	91278912	-7.724	49767210	-7.527	73950609	-7.246
59229857	-7.793	69612311	-7.723	49767248	-7.523	58857486	-7.218
71121204	-7.793	58857502	-7.717	5746640	-7.521	58581736	-7.201
59239975	-7.792	49767207	-7.714	15947382	-7.515	91798577	-7.201
72241236	-7.792	24990149	-7.702	89390251	-7.506	49767214	-7.171
71090872	-7.791	71090869	-7.698	24990148	-7.498	59229865	-7.136
49767231	-7.788	71090875	-7.692	89880716	-7.497	74223349	-7.115
59239954	-7.786	49767213	-7.69	58853328	-7.489	69647836	-7.114
72241224	-7.786	58857546	-7.69	58857510	-7.489	59229852	-7.108
49767221	-7.784	89880708	-7.685	49767227	-7.485	9985456	-7.093
15947587	-7.779	59805723	-7.675	49767129	-7.472	53392193	-7.069
58853337	-7.779	59229806	-7.672	69665357	-7.465	53392481	-7.057
59805724	-7.775	72241216	-7.664	73950612	-7.465	49767229	-7.042
86579835	-7.774	74223274	-7.662	59672555	-7.458	49767258	-7.027
89390729	-7.774	49767239	-7.656	25050509	-7.456	46849631	-7.02
91536771	-7.772	24990147	-7.652	49767237	-7.456	53392270	-7.02
74223221	-7.771	15979900	-7.649	59229829	-7.445	58853338	-7.003
49767257	-7.77	58853325	-7.638	73950613	-7.445	53392394	-6.985
49767256	-7.767	49767249	-7.636	90998990	-7.428	59239931	-6.869
11421514	-7.764	25050510	-7.628	91248828	-7.419	69305090	-6.837
74223275	-7.762	11713126	-7.614	49767140	-7.418	69647835	-6.795
49767143	-7.761	6319952	-7.608	9958970	-7.402	69665358	-6.369
15979783	-7.76	90770320	-7.606	49767128	-7.389		
69612310	-7.759	59672556	-7.605	73950606	-7.374		
73357431	-7.759	91290580	-7.597	53392271	-7.341		
11990660	-7.747	71090866	-7.596	69331985	-7.338		
74223217	-7.747	73950605	-7.584	59229841	-7.313		
101857334	-7.743	74223276	-7.564	71219312	-7.305		
76961808	-7.743	59672554	-7.559	10414940	-7.301		
49767263	-7.737	49767217	-7.555	10030219	-7.294		
15947275	-7.733	91380182	-7.555	11226668	-7.27		

Table S2. Lipophilicity/Partition coefficient (QPlogPo/w) of Bedaquiline analogues predicted by QikProp, Schrodinger 9.0.

CID Code	QPlogPo/w	CID Code	QPlogPo/w	CID Code	QPlogPo/w
Bedaquiline	**7.832**	49767126	7.411	69305090	6.722
58853338	7.824	49767128	7.394	58853328	6.7
59805724	7.824	49767140	7.358	76961808	6.67
49767213	7.814	66647123	7.338	101857334	6.638
49767143	7.806	91248828	7.336	24990147	6.405
15979783	7.799	91536771	7.336	89390729	6.388
49767218	7.79	49767210	7.304	59229857	6.244
49767129	7.778	49767237	7.29	49767227	6.138
49767207	7.753	5746640	7.288	69665358	6.086
49767260	7.738	10325030	7.282	73950613	6.086
59805723	7.734	86579835	7.277	59239931	5.574
53392481	7.714	73950612	7.276		
49767239	7.703	46849631	7.262		
69647835	7.69	58857510	7.262		
11421514	7.686	53392270	7.224		
15947587	7.685	73357431	7.22		
49767257	7.667	49767258	7.165		
68276628	7.655	53392394	7.155		
73950610	7.642	91290580	7.155		
90998990	7.635	74223349	7.151		
74223221	7.603	49767229	7.109		
74223217	7.589	58857486	7.097		
91380182	7.573	53392271	7.079		
58581736	7.564	69665357	7.079		
91798577	7.564	24990149	7.076		
49767214	7.561	91278912	7.066		
69331985	7.54	11713126	7.065		
73950606	7.54	6319952	7.052		
9958970	7.518	90770320	7.023		
68452953	7.511	73950605	6.995		
11226668	7.463	58857502	6.958		
73950609	7.455	58857546	6.938		
15947275	7.444	89880708	6.897		
10414940	7.429	59229865	6.778		
10030219	7.414	24990148	6.75		

Table S3. Glide SP docking score of the Bedaquiline analogues against Mycobacterial ATP Synthase

CID Code	Docking score	glide gscore	glide emodel	CID Code	Docking score	glide gscore	glide emodel
15947587	-5.636	-5.64	-65.052	59239931	-4.907	-4.908	-49.169
49767237	-5.593	-5.597	-65.642	49767239	-4.898	-4.902	-61.238
73950609	-5.576	-5.577	-66.983	66647123	-4.875	-4.879	-54.918
10030219	-5.503	-5.505	-65.332	15979783	-4.865	-4.869	-53.872
49767128	-5.501	-5.497	-64.74	91290580	-4.821	-4.892	-55.249
73950610	-5.488	-5.491	-62.115	91380182	-4.81	-4.88	-52.241
91248828	-5.404	-5.475	-56.017	9958970	-4.773	-4.777	-55.518
74223217	-5.377	-5.379	-60.1	24990147	-4.747	-4.749	-52.228
73950613	-5.375	-5.378	-63.21	59805723	-4.726	-4.727	-56.005
Bedaquiline	-5.357	-5.361	-63.928	10325030	-4.723	-4.724	-55.097
73950606	-5.344	-5.347	-65.668	91278912	-4.644	-4.714	-54.214
49767140	-5.301	-5.304	-63.485	15947275	-4.621	-4.623	-54.08
49767126	-5.272	-5.276	-61.409	69665358	-4.561	-4.564	-47.978
90998990	-5.224	-5.227	-60.984	49767207	-4.476	-4.48	-56.348
10414940	-5.214	-5.218	-63.877	59229865	-4.436	-4.569	-57.445
58857486	-5.204	-5.209	-55.14	24990148	-4.397	-4.398	-49.324
49767129	-5.2	-5.203	-64.922	59229857	-4.38	-4.413	-46.815
11713126	-5.138	-5.142	-62.543	11421514	-4.377	-5.191	-56.632
6319952	-5.138	-5.142	-62.543	89880708	-4.33	-4.337	-44.732
90770320	-5.135	-5.206	-57.48	58857510	-4.31	-4.315	-51.429
91536771	-5.132	-5.132	-61.194	68452953	-4.221	-4.292	-49.051
49767227	-5.093	-5.093	-61.213	24990149	-4.219	-4.22	-49.231
49767210	-5.087	-5.09	-57.844	73357431	-4.17	-4.173	-44.482
69305090	-5.086	-5.089	-61.39	76961808	-4.115	-4.116	-48.384
69665357	-5.081	-5.152	-59.595	49767260	-3.992	-4.21	-40.054
73950612	-5.081	-5.152	-59.595	74223349	-3.925	-3.928	-39.04
101857334	-5.062	-5.063	-59.856	49767213	-3.876	-3.878	-47.481
5746640	-5.044	-5.047	-59.185	69331985	-3.816	-4.005	-48.174
89390729	-5.025	-5.026	-63.838	68276628	-3.76	-4.354	-52.562
58857546	-5.011	-5.015	-55.461	11226668	-3.598	-4.412	-53.809
49767214	-4.983	-4.987	-50.162	49767229	-3.566	-3.575	-43.709
71090872	-4.973	-4.996	-56.8	58853328	-3.537	-4.351	-52.734
49767143	-4.946	-4.95	-57.318	46849631	-3.402	-3.402	-41.672
73950605	-4.938	-4.941	-55.944	53392270	-3.402	-3.402	-41.672

Table S3. *Continue…*

CID Code	Docking score	glide gscore	glide emodel	CID Code	Docking score	glide gscore	glide emodel
58581736	-4.919	-4.923	-54.303	53392271	-3.337	-3.337	-42.181
91798577	-4.919	-4.923	-54.303	69647835	-3.305	-3.305	-44.163
58857502	-4.907	-4.911	-52.033	49767258	-3.178	-3.66	-48.61
53392394	-3.044	-3.044	-36.848	49767257	-2.527	-2.873	-36.925
49767218	-3.038	-3.047	-37.774	86579835	-2.115	-3.281	-38.886
53392481	-2.7	-2.7	-36.321	74223221	-1.155	-2.622	-37.703

Table S4. Glide SP docking score of the diastereomers of virtually screened hit against *Mycobacterial* ATP Synthase

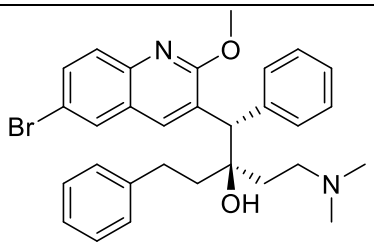
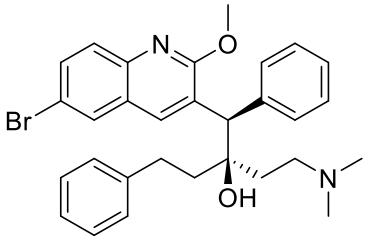
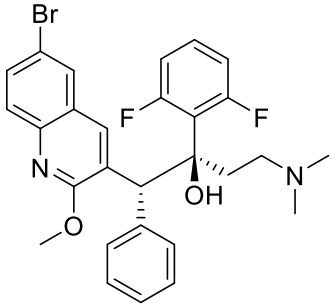
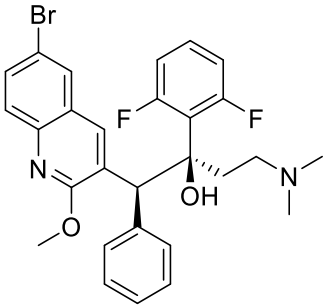
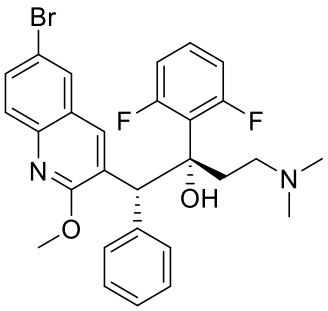
Compound Code	Diastereomers	Docking score	Glide gscore	Glide emodel
CID 15947587		-5.636	-5.64	-65.052
		-5.185	-5.186	-55.839
CID 49767237		-5.593	-5.597	-65.642
		-5.058	-5.062	-55.212
		-4.937	-4.941	-61.051

Table S4. *Continue…*

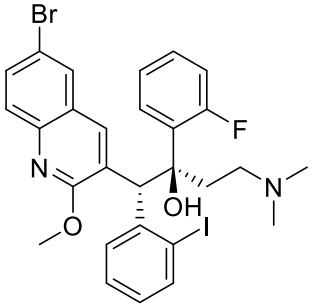
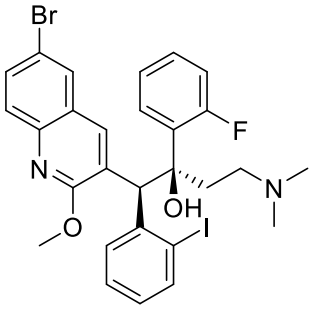
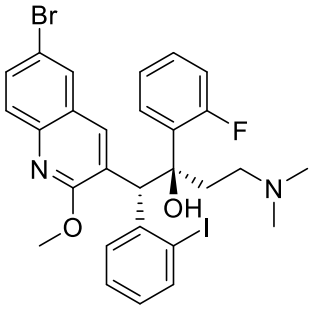
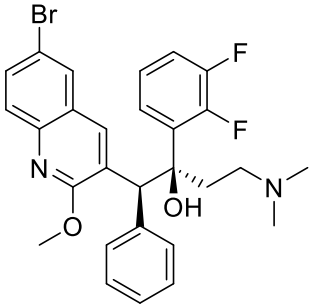
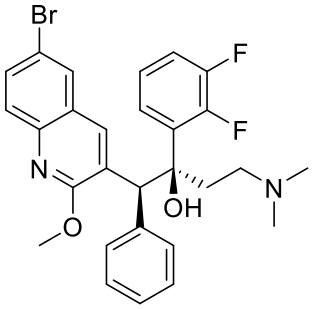
Compound Code	Diastereomers	Docking score	Glide gscore	Glide emodel
CID 73950609		-5.576	-5.577	-66.983
		-5.249	-5.253	-51.287
		-5.100	-5.104	-63.541
CID 10030219		-5.503	-5.497	-64.74
		-4.408	-4.412	-49.904

Table S4. *Continue…*

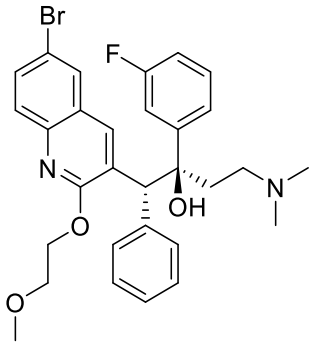
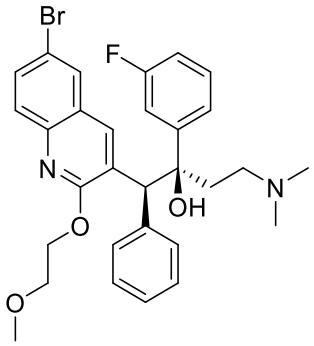
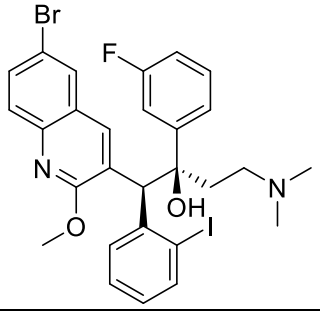
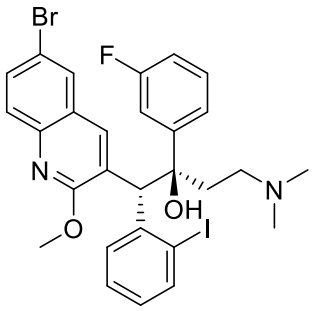
Compound Code	Diastereomers	Docking score	Glide gscore	Glide emodel
CID 49767128		-5.501	-5.505	-65.332
		-4.300	-4.304	-49.091
CID 73950610		-5.488	-5.491	-62.115
		-5.470	-5.474	-62.991

Table S4. *Continue…*

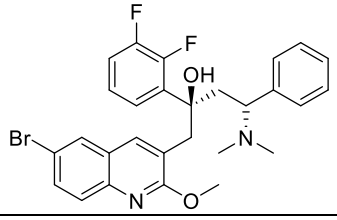
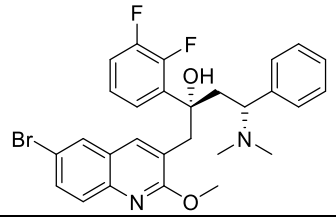
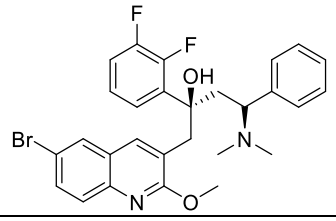
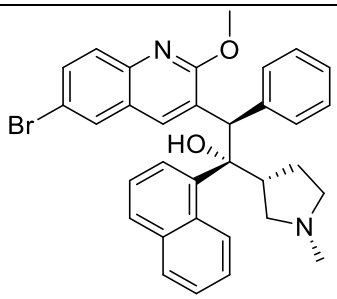
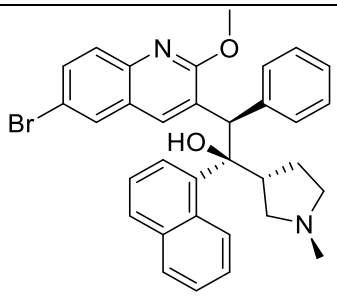
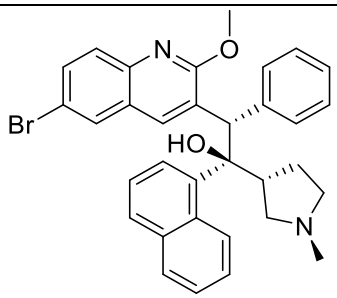
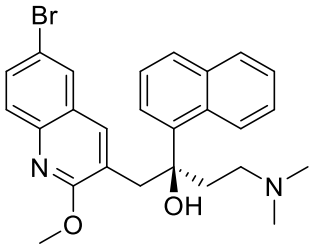
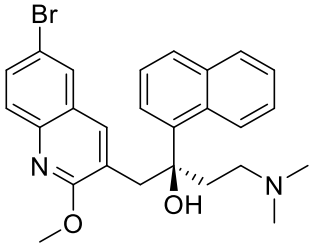
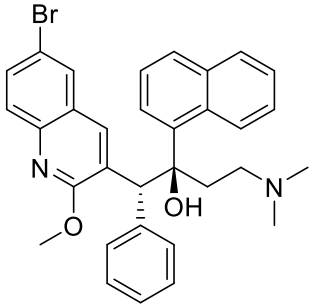
Compound Code	Diastereomers	Docking score	Glide gscore	Glide emodel
CID 91248828		-5.404	-5.475	-56.017
		-4.143	-4.213	-48.371
		-3.373	-3.443	-39.758
CID 74223217		-5.377	-5.379	-60.10
		-3.949	-3.950	-42.269
		-3.897	-3.899	-43.375

Table S4. *Continue…*

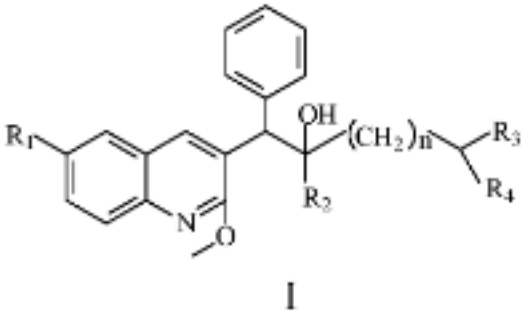
Compound Code	Diastereomers	Docking score	Glide gscore	Glide emodel
CID 73950613		-5.375	-5.378	-63.21
		-4.561	-4.564	-47.978
Bedaquiline		-5.357	-5.361	-63.928

Novelity of Compounds

Among the 9 virtually screened hits CID 73950609, CID 73950610 and CID 91248828 were novel for the anti-mycobacterial activity

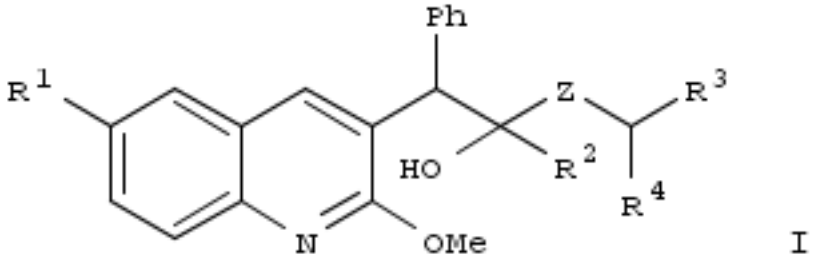
1. Preparation of quinoline derivatives as antitubercular agents

By Deng, Jie; Lei, Huangshu; Wang, Weibo; Liu, Caiping; Ye, Wenrun; Xu, Liyan; Zhou, Changbing; Zhang, Guoyao; Zou, Yanye; He, Zhiqin
From PCT Int. Appl. (2015), WO 2015096611 A1 20150702, Language: Chinese, Database: CAPLUS



I

The invention relates to quinoline derivs. of formula I, method for their prepn. and their use in the treatment of tubercule bacillus infection. Compds. of formula I, wherein R^1 is H, halo, OH, alkyl, etc.; R^2 is (un)substituted Ph, naphthyl, heterocycle, etc.; R^3 and R^4 together form satd. or unsatd. heterocycle; and Z is $(CH_2)_{0-4}$; and their optical isomers, racemates, diastereomers, pharmaceutically acceptable salts or solvates, are claimed. Example compd. II was prepd. by addn. reaction of 3-benzyl-6-bromo-2-methoxyquinoline with [1-(diphenylmethyl)-3-azetidinyl]phenylmethanone. All the invention compds. were evaluated for their antitubercular activity. From the assay, it was detd. that example compd. II exhibited MIC value of ≥ 8 μg / mL.



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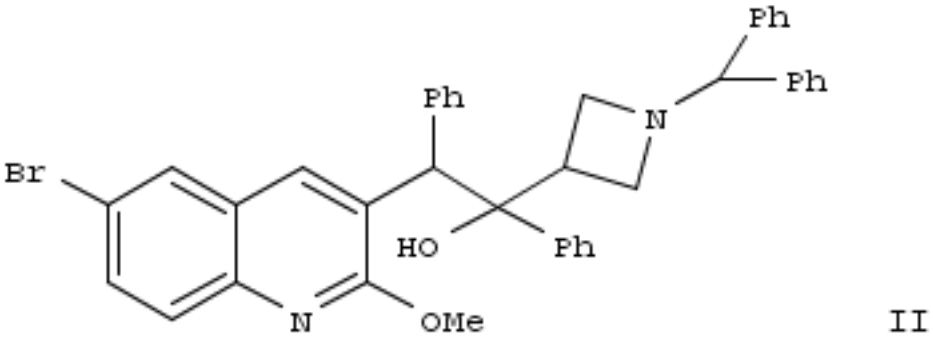


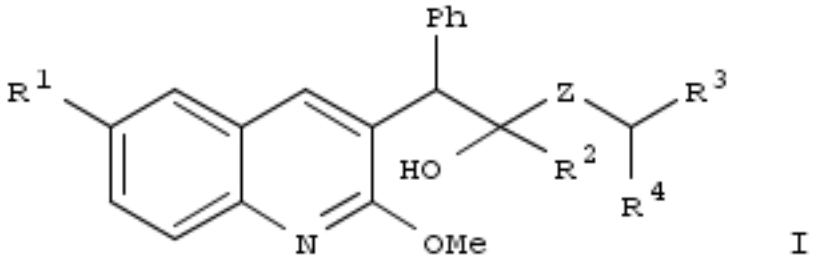
II

~0 Citings

2. Preparation of quinoline derivatives as antitubercular agents

By Deng, Jie; Lei, Huangshu; Wang, Weibo; Liu, Caiping; Ye, Wenrun; Xu, Liyan; Zhou, Changbing; Zhang, Guoyao; Zou, Yanye; He, Zhiqin
From Faming Zhuanli Shenqing (2014), CN 103664877 A 20140326, Language: Chinese, Database: CAPLUS

The invention relates to quinoline derivs. of formula I, method for their prepn. and their use in the treatment of tubercule bacillus infection. Compds. of formula I, wherein R^1 is H, halo, OH, alkyl, etc.; R^2 is (un)substituted Ph, naphthyl, heterocycle, etc.; R^3 and R^4 together form satd. or unsatd. heterocycle; and Z is $(CH_2)_{0-4}$; and their optical isomers, racemates, diastereomers, pharmaceutically acceptable salts or solvates, are claimed. Example compd. II was prepd. by addn. reaction of 3-benzyl-6-bromo-2-methoxyquinoline with [1-(diphenylmethyl)-3-azetidinyl]phenylmethanone. All the invention compds. were evaluated for their antitubercular activity. From the assay, it was detd. that example compd. II exhibited MIC value of ≥ 8 μg / mL.



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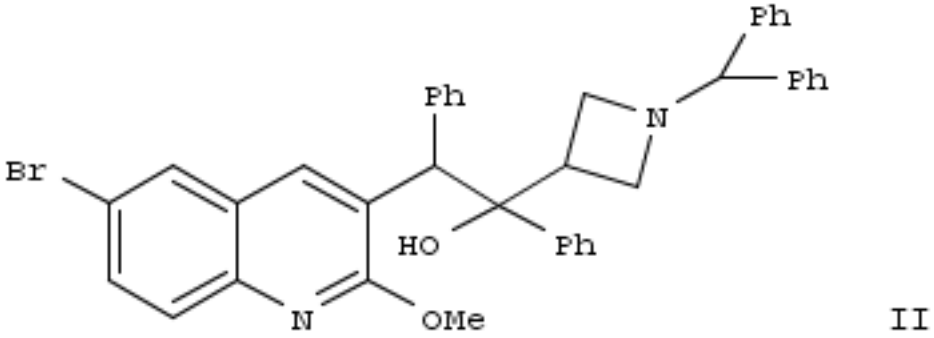


II

~1 Citing

1. Diarylquinolines, synthesis pathways and quantitative structure-activity relationship studies leading to the discovery of TMC207

By Guillemont, Jerome; Meyer, Christophe; Poncelet, Alain; Bourdrez, Xavier; Andries, Koen
From Future Medicinal Chemistry (2011), 3(11), 1345-1360. Language: English, Database: CAPLUS, DOI:10.4155/fmc.11.79

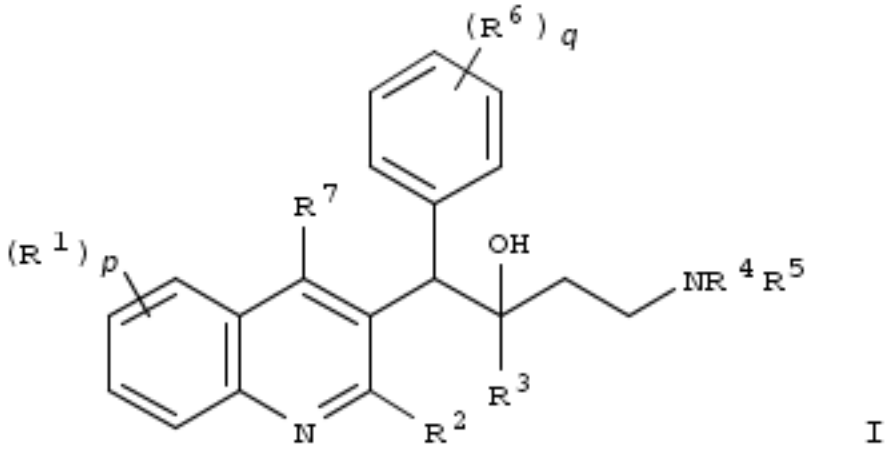
The emergence of multidrug-resistant strains of Mycobacterium tuberculosis and resistance to current anti-TB drugs call for the discovery and development of new effective anti-TB drugs. TMC207 is the lead candidate of a novel class of antimycobacterial agents, the diarylquinolines, which specifically inhibit mycobacterial ATP synthase and displays high activity against both drug-susceptible and multidrug-resistant strains of Mycobacterium tuberculosis. This article covers both synthesis pathways as well as qual. and quant. analyses of the structure-activity relationships of the diarylquinoline series on Mycobacterium smegmatis activity.

~43 Citings

2. Preparation of aminohydroxyphenylbutylquinolines as antibacterials.

By Andries, Koenraad Jozef Lodewijk Marcel; Koul, Anil; Guillemont, Jerome Emile Georges; Pasquier, Elisabeth Therese Jeanne; Lancois, David Francis Alain
From PCT Int. Appl. (2006), WO 2006131519 A1 20061214, Language: English, Database: CAPLUS

Use of title compds. [I; R^1 = H, halo, polyhaloalkyl, alkyl, hydroxyalkyl, alkoxy, Ar, Het; p, q = 1, 2; R^2 = alkoxy, alkoxyalkoxy, alkylthio; R^3 = alkyl, Ar, Het, Het1; R^4, R^5 = H, alkyl, benzyl; R^4R^5N = (substituted) pyrrolidinyl, pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, imidazolinyl, pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, piperidinyl, pyridinyl, piperazinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl, thiomorpholinyl; R^6 = H, halo, polyhaloalkyl, alkyl, alkoxy, alkylthio; 2 vicinal R^6 may = CH:CHCH:CH; R^7 = H, alkyl, Ar, Het, Het1; Ar = (substituted) Ph, naphthyl, acenaphthyl, 1,2-dihydroacenaphthyl, tetrahydronaphthyl; Het = (substituted) piperidyl, pyrrolyl, N-phenoxypiperidyl, pyrazolyl, triazolyl, imidazolyl, furyl, pyridyl, pyrimidyl, pyrazinyl, etc.; Het1 = (substituted) quinolyl, quinoxalinyl, indolyl, benzimidazolyl, benzofuryl, benzothienyl, 2,3-dihydrobenzodioxinyl, etc.; with provisos], for manuf. of a medicament for treatment of bacterial infection is claimed. Thus, a diastereomer of title compd. (II) (prepn. outlined) showed an IC_{90} = 10.8 μg/mL against Streptococcus mutans ATCC33402.



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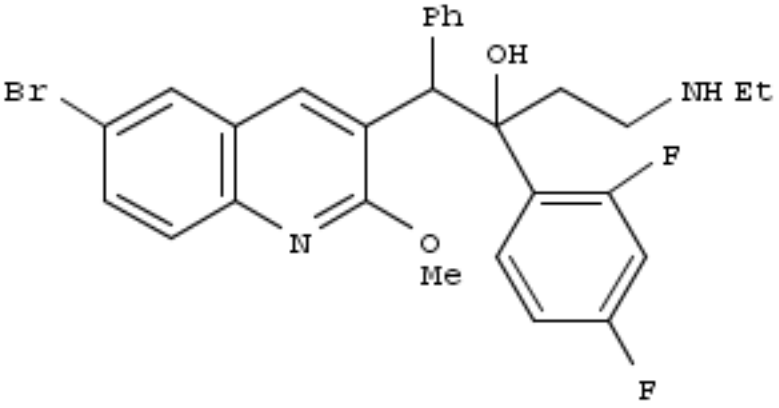


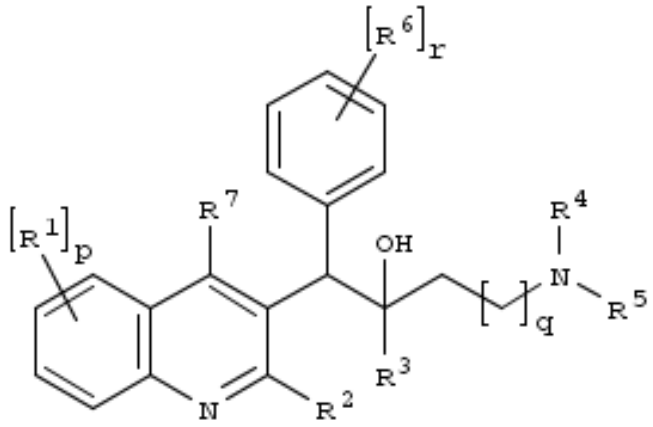
II

~10 Citings

3. Preparation of quinoline derivatives and their use as mycobacterial inhibitors

By Koul, Anil; Andries, Koenraad Jozef Lodewijk Marcel
From Can. Pat. Appl. (2006), CA 2529265 A1 20060624, Language: English, Database: CAPLUS

The title compds. [I or II; R^1 = H, halo, haloalkyl, CN, etc.; p = 0-4; R^2 = H, OH, thio, alkoxy, etc.; R^3 = alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl; q = 0-4; R^4, R^5 = H, alkyl, CH_2Ph; or NR^4R^5 = pyrrolidinyl, imidazolyl, triazolyl, etc.; R^6 = H, halo, haloalkyl, etc.; or two vicinal R^6 may be taken together to form CH:CHCH:CH; r = 0-5; R^7 = H, alkyl, aryl, heteroaryl; R^8 = H, alkyl; R^9 = oxo; or R^8 and R^9 together form NCH:CH] which are useful for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as Mycobacterium tuberculosis, M. bovis, M. avium and M. marinum, were prepd. In particular, compds. are claimed in which, independently from each other, R^1 = Br, p = 1, R^2 = alkyloxy, R^3 = (un)substituted naphthyl or Ph, q = 1, R^4 and R^5 each independently = H, Me or Et, R^6 = H, r = 0-1 and R^7 = H. E.g., a multi-step synthesis of III which showed MIC of 0.34 μg/mL and pIC_{50} of 8.5 against M. tuberculosis and M. smegmatis, resp., was given. Also claimed is a compn. comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amt. of the claimed compds. I, the use of the claimed compds. or compns. for the manuf. of a medicament for the treatment of mycobacterial diseases and a process for prepg. the claimed compds.



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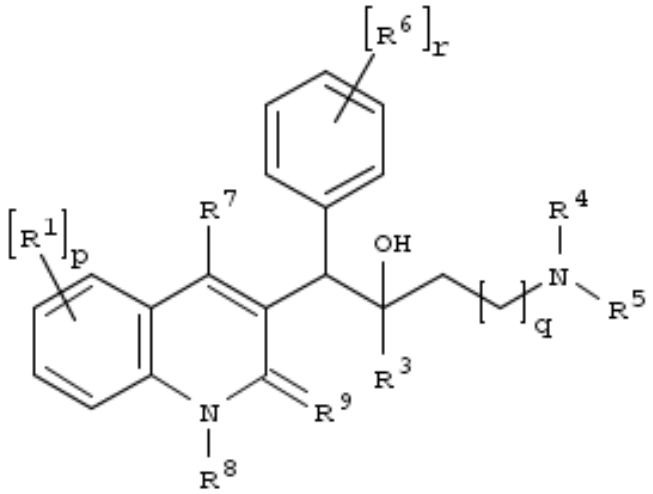
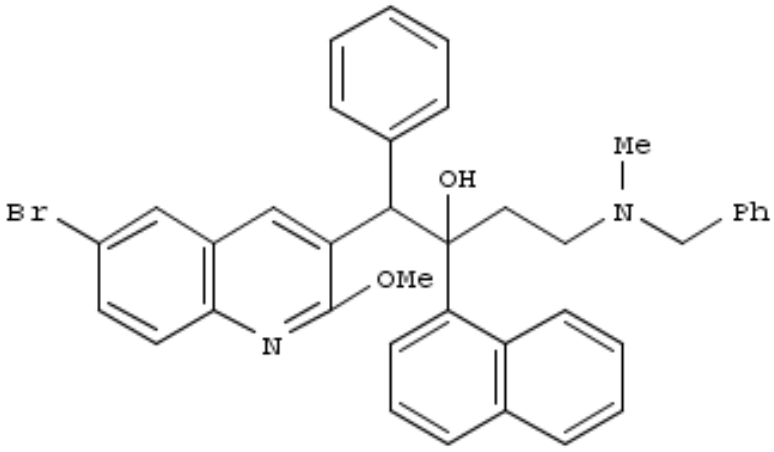


II



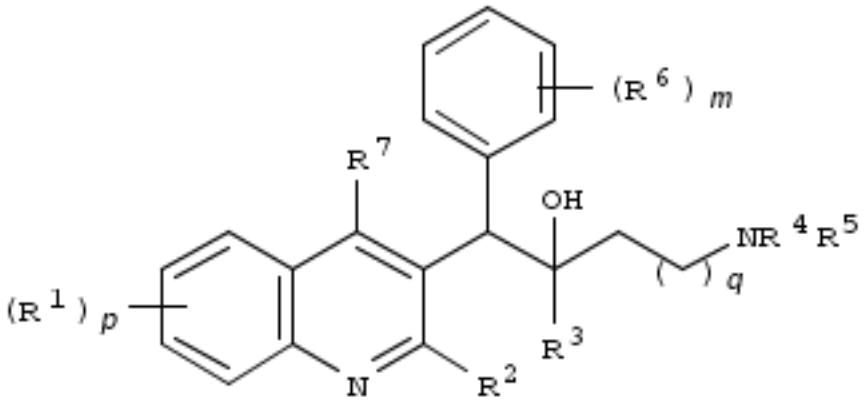
III

~12 Citings

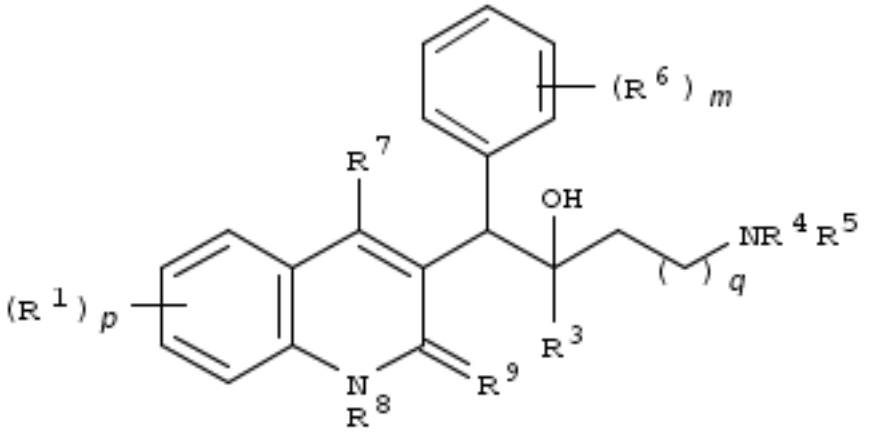
4. Preparation of aminohydroxyaralkylquinolines for the treatment of drug resistant mycobacterial diseases

By Andries, Koenraad Jozef Lodewijk Marcel; Van Gestel, Jozef Frans Elisabetha
From PCT Int. Appl. (2005), WO 2005117875 A1 20051215, Language: English, Database: CAPLUS

Use of title compds. [I, II; R^1 = H, halo, haloalkyl, cyano, OH, aryl, heterocyclyl, alkyl, alkoxy, alkylthio, alkoxyalkyl, etc.; p = 1-4; R^2 = H, OH, SH, alkoxy, alkylthio, alkylamino, etc.; R^3 = alkyl, aryl, heterocyclyl, aralkyl, heterocyclylalkyl; q = 0-4; R^4, R^5 = H, alkyl, $PhCH_2$; R^4R^5N = (substituted) pyrrolidinyl, imidazolyl, morpholinyl, thiomorpholinyl, pyrazinyl, etc.; R^6 = H, halo, haloalkyl, OH, aryl, alkyl, alkoxy, alkylthio, aralkyl, etc.; 2 vicinal R^6 = CH:CHCH:CH; m = 1-5; R^7 = H, alkyl, aryl, heterocyclyl; R^8 = H, alkyl; R^9 = O; R^8R^9 = NCH:CH] for prepn. of a medicament for treatment of an infection with a drug resistant Mycobacterium strain is claimed. Title compds. showed min. inhibitory concns. of 0.06-0.12 mg/L against isoniazid-resistant M. tuberculosis.



I



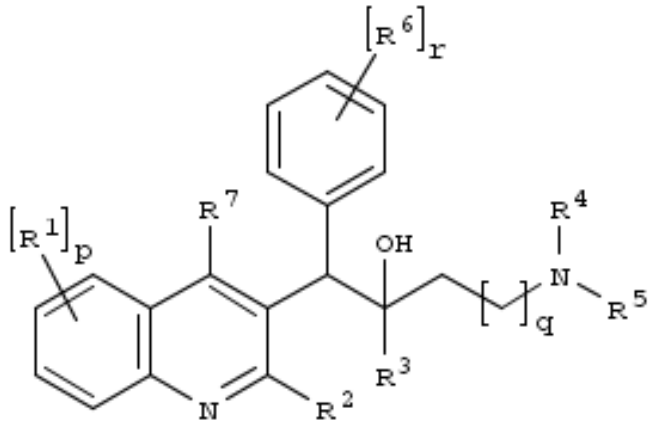
II

~25 Citings

5. Preparation of quinoline derivatives and their use as mycobacterial inhibitors

By Van Gestel, Jozef Frans Elisabetha; Guillemont, Jerome Emile Georges; Venet, Marc Gaston; Poignet, Herve Jean Joseph; Decrane, Laurence Francoise Bernadette; Vernier, Daniel F. J.; Odds, Frank Christopher
From U.S. Pat. Appl. Publ. (2005), US 20050148581 A1 20050707, Language: English, Database: CAPLUS

The title compds. [I or II; R^1 = H, halo, haloalkyl, CN, etc.; p = 0-4; R^2 = H, OH, thio, alkoxy, etc.; R^3 = alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl; q = 0-4; R^4, R^5 = H, alkyl, CH_2Ph; or NR^4R^5 = pyrrolidinyl, imidazolyl, triazolyl, etc.; R^6 = H, halo, haloalkyl, etc.; or two vicinal R^6 may be taken together to form CH:CHCH:CH; r = 0-5; R^7 = H, alkyl, aryl, heteroaryl; R^8 = H, alkyl; R^9 = oxo; or R^8 and R^9 together form NCH:CH] which are useful for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as Mycobacterium tuberculosis, M. bovis, M. avium and M. marinum, were prepd. In particular, compds. are claimed in which, independently from each other, R^1 = Br, p = 1, R^2 = alkyloxy, R^3 = (un)substituted naphthyl or Ph, q = 1, R^4 and R^5 each independently = H, Me or Et, R^6 = H, r = 0-1 and R^7 = H. E.g., a multi-step synthesis of III which showed MIC of 0.34 μg/mL and pIC_{50} of 8.5 against M. tuberculosis and M. smegmatis, resp., was given. Also claimed is a compn. comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amt. of the claimed compds. I, the use of the claimed compds. or compns. for the manuf. of a medicament for the treatment of mycobacterial diseases and a process for prepg. the claimed compds.



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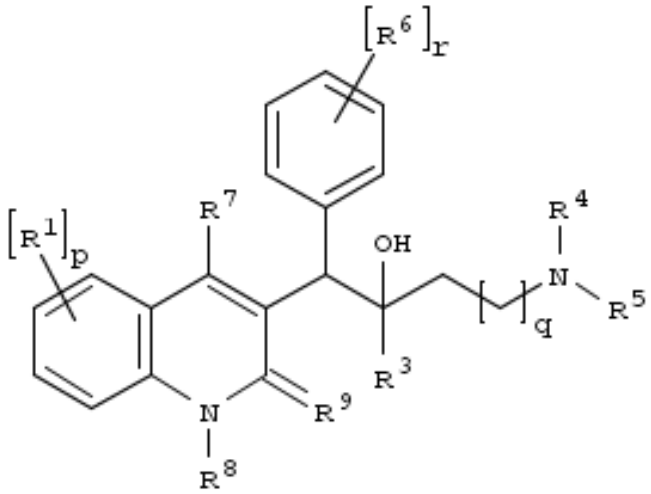

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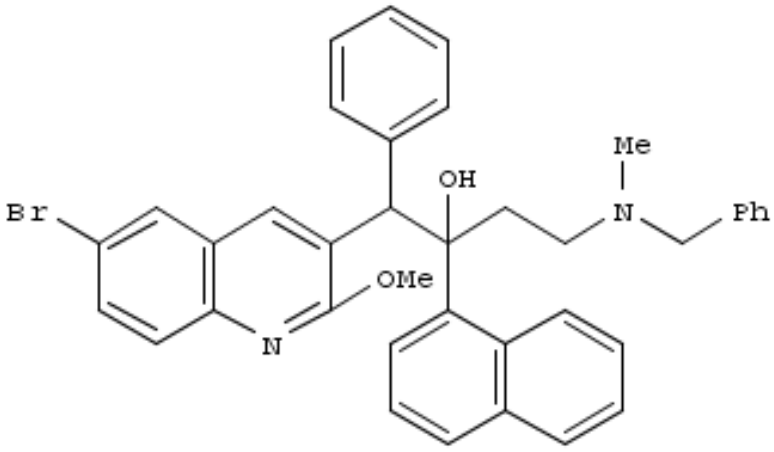


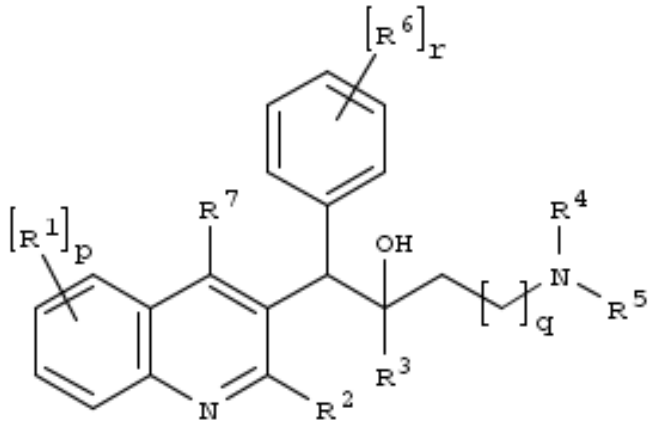
III

~12 Citings

6. Preparation of quinoline derivatives and their use as mycobacterial inhibitors

By Guillemont, Jerome Emile Georges; Van Gestel, Jozef Frans Elisabetha; Venet, Marc Gaston; Poignet, Herve Jean Joseph; Decrane, Laurence Francoise Bernadette; Vernier, Daniel F. J.
From PCT Int. Appl. (2004), WO 2004011436 A1 20040205, Language: English, Database: CAPLUS

The title compds. [I or II; R^1 = H, halo, haloalkyl, CN, etc.; p = 0-4; R^2 = H, OH, thio, alkoxy, etc.; R^3 = alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl; q = 0-4; R^4, R^5 = H, alkyl, CH_2Ph; or NR^4R^5 = pyrrolidinyl, imidazolyl, triazolyl, etc.; R^6 = H, halo, haloalkyl, etc.; or two vicinal R^6 may be taken together to form C:CC:C; r = 0-5; R^7 = H, alkyl, aryl, heteroaryl; R^8 = H, alkyl; R^9 = oxo; or R^8 and R^9 together form NCH:CH] which are useful for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as Mycobacterium tuberculosis, M. bovis, M. avium and M. marinum, were prepd. In particular, compds. are claimed in which, independently from each other, R^1 = Br, p = 1, R^2 = alkyloxy, R^3 = (un)substituted naphthyl or Ph, q = 1, R^4 and R^5 each independently = H, Me or Et, R^6 = H, r = 0-1 and R^7 = H. E.g., a multi-step synthesis of III which showed MIC of 0.34 μg/mL and pIC_{50} of 8.5 against M. tuberculosis and M. smegmatis, resp., was given. Also claimed is a compn. comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amt. of the claimed compds. I, the use of the claimed compds. or compns. for the manuf. of a medicament for the treatment of mycobacterial diseases and a process for prepg. the claimed compds.



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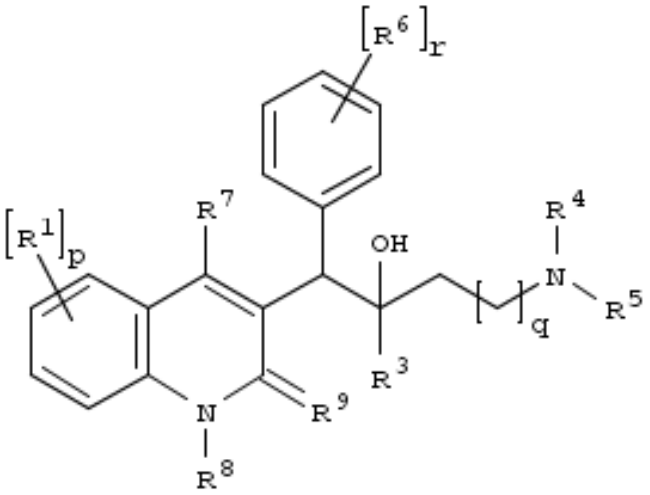

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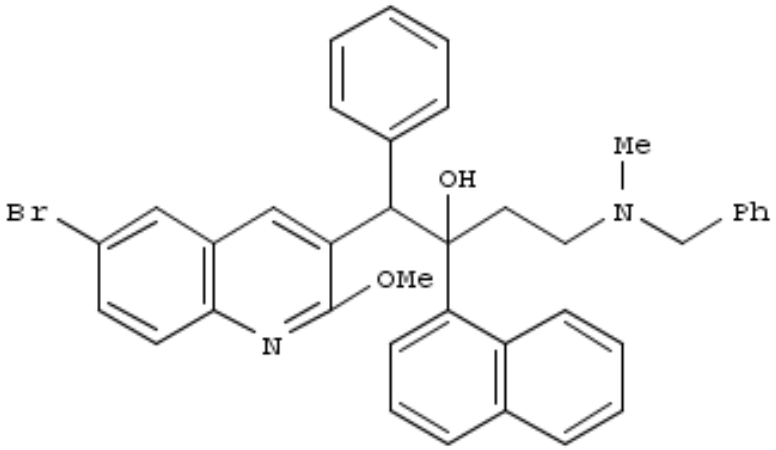


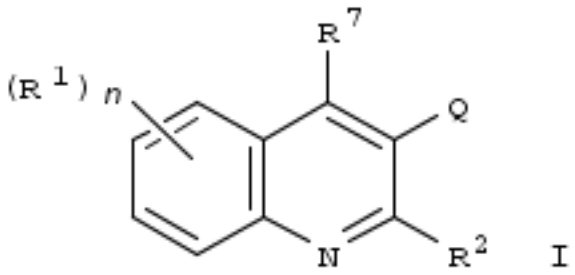
III

~58 Citings

1. Antibacterial quinoline derivatives and their preparation and use in the treatment of bacterial infection

By Guillemont, Jerome Emile Georges; Dorange, Ismet; Andries, Koenraad Jozef Lodewijk Marcel; Koul, Anil
From PCT Int. Appl. (2008), WO 2008068266 A1 20080612, Language: English, Database: CAPLUS

The invention relates to substituted quinoline derivs. according to the general formula I and II: including any stereochem. isomeric form thereof, N-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof. The claimed compds. are useful for the treatment of a bacterial infection. Also claimed is a compn. comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amt. of the claimed compds., the use of the claimed compds. or compns. for the manuf. of a medicament for the treatment of a bacterial infection and a process for prepg. the claimed compds. Compds. of formula I and II wherein Q is substituted aminoalk-1-enyl, substituted aminoalk-2-enyl, substituted 2-(aminoalkyl)alk-2-enyl; n is 1, 2, 3 and 4; R^1 is H, CN, CHO, CO, halo, (halo)alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OH, alkoxy, etc.; R^2 is H, alkoxy, aryl, aryloxy, OH, mercapto, , etc.; R^7 is H, halo, alkyl, aryl, and monocyclic heterocycle; R^8 is H and alkyl; R^9 is oxo; R^8R^9 taken together to form CH=CH-N=; and their stereochem. isomeric forms, N-oxides, pharmaceutically acceptable salts, and solvates thereof, are claimed. Example compd. III was prepd. by a general procedure (procedure given). All the invention compds. were evaluated for their antibacterial activity. From the assay, it was detd. that compd. III exhibited IC_{90} value of 1.65 μG/mL.



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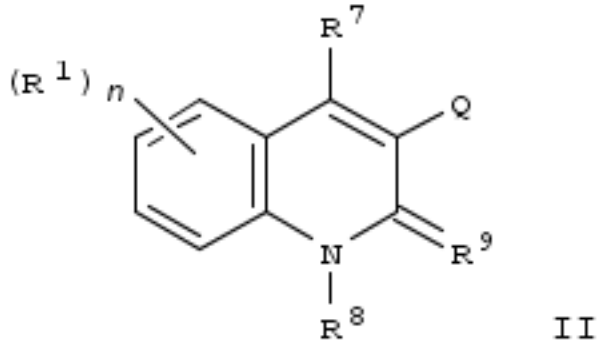

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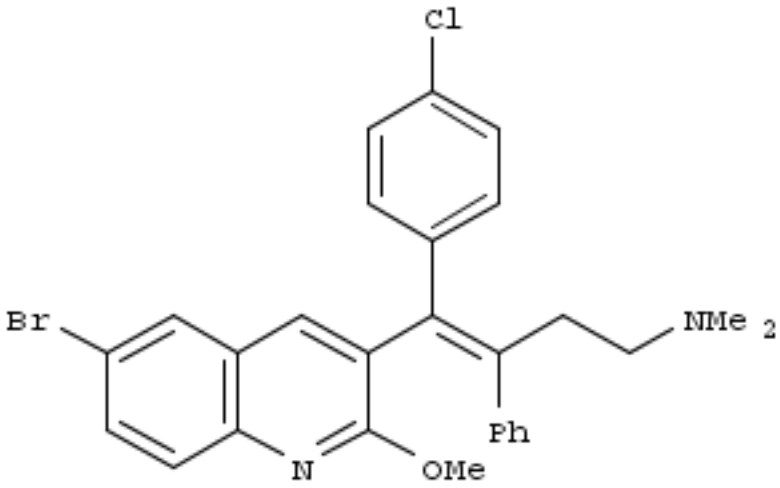


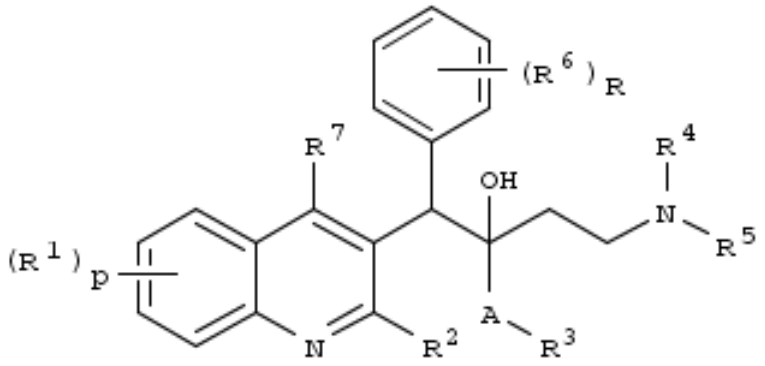
III

~1 Citing

2. Quinoline derivatives as antibacterial agents and their preparation, pharmaceutical compositions and use in the treatment of bacterial infections

By Andries, Koenraad Jozef Lodewijk Marcel; Koul, Anil; Guillemont, Jerome Emile Georges; Motte, Magali Madeleine Simone
From PCT Int. Appl. (2007), WO 2007000436 A1 20070104, Language: English, Database: CAPLUS

Use of a compd. for the manuf. of a medicament for the treatment of a bacterial infection provided that the bacterial infection is other than a Mycobacterial infection, said compd. being a compd. of formula I or II a pharmaceutically acceptable acid or base addn. salt thereof, a stereochem. isomeric form thereof, a tautomeric form thereof or a N-oxide form thereof. Compds. of formula I and II wherein R^1 is H, halo, haloalkyl, CN, OH, (un)substituted aryl, (un)substituted heterocyclyl, (un)substituted alkyl, etc,; p is 1, 2, 3, and 4; R^2 is H, OH, mercapto, alkyloxy(alkyloxy), alkylthio, etc.; R^3 is (un)substituted aryl and (un)substituted heterocyclyl; R^4 and R^5 are independently H, (un)substituted alkyl, benzyl; R^4R^5 together with N may forma a heterocycle; R^6 is H, halo, haloalkyl, alkoxy, (un)substituted aryl, (un)substituted alkyl, etc.; r is 1, 2, 3, 4, and 5; R^7 is H, (un)substituted alkyl, (un)substituted aryl and (un)substituted heterocyclyl; R^8 is H, and (un)substituted alkyl, R^9 is oxo; R^8R^9 together may form the radical CH=CH-N=; A is (un)branched C_{1-6} alkyl; and their pharmaceutically acceptable acid and base salts, stereochem. isomeric forms, tautomeric forms, and N-oxides thereof, are claimed. Several of these compds. are also claimed as such. Further the combination of the above compds. with other antibacterial agents is described. Example compd. III was prepd. by addn. of 3-benzyl-2-methoxy-6-methylquinoline to 1-(dimethylamino)-5-phenyl-3-pentanone. All the invention compds. were evaluated for their antibacterial activity. From the assay, it was detd. that compd. III exhibited IC_{90} values in the range of 1.9 - 37.2 μg/mL against various bacteria.



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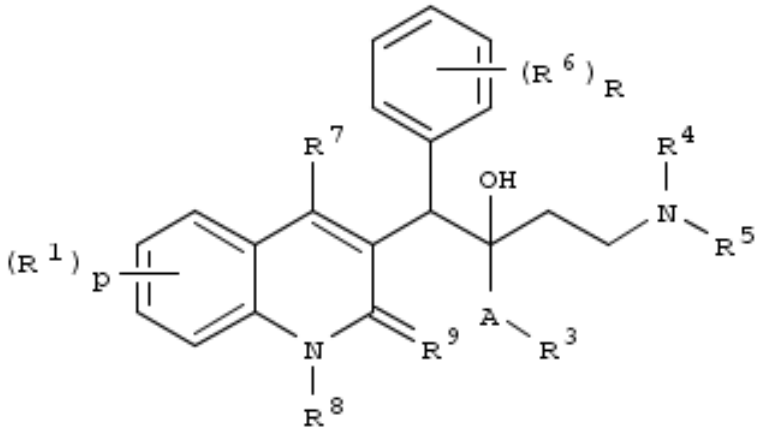

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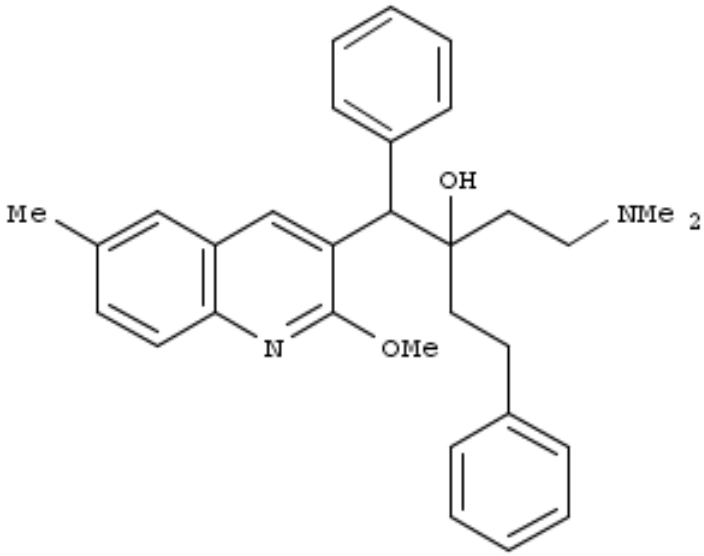


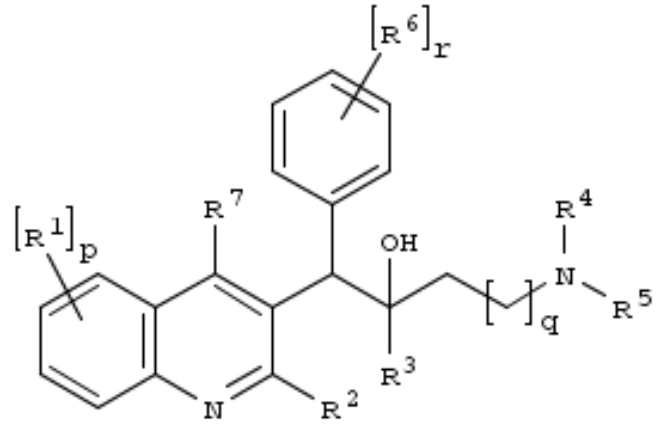
III

~1 Citing

3. Preparation of quinoline derivatives and their use as mycobacterial inhibitors

By Koul, Anil; Andries, Koenraad Jozef Lodewijk Marcel
From Can. Pat. Appl. (2006), CA 2529265 A1 20060624, Language: English, Database: CAPLUS

The title compds. [I or II; R^1 = H, halo, haloalkyl, CN, etc.; p = 0-4; R^2 = H, OH, thio, alkoxy, etc.; R^3 = alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl; q = 0-4; R^4, R^5 = H, alkyl, CH_2Ph; or NR^4R^5 = pyrrolidinyl, imidazolyl, triazolyl, etc.; R^6 = H, halo, haloalkyl, etc.; or two vicinal R^6 may be taken together to form CH:CHCH:CH; r = 0-5; R^7 = H, alkyl, aryl, heteroaryl; R^8 = H, alkyl; R^9 = oxo; or R^8 and R^9 together form NCH:CH] which are useful for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as Mycobacterium tuberculosis, M. bovis, M. avium and M. marinum, were prepd. In particular, compds. are claimed in which, independently from each other, R^1 = Br, p = 1, R^2 = alkyloxy, R^3 = (un)substituted naphthyl or Ph, q = 1, R^4 and R^5 each independently = H, Me or Et, R^6 = H, r = 0-1 and R^7 = H. E.g., a multi-step synthesis of III which showed MIC of 0.34 μg/mL and pIC_{50} of 8.5 against M. tuberculosis and M. smegmatis, resp., was given. Also claimed is a compn. comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amt. of the claimed compds. I, the use of the claimed compds. or compns. for the manuf. of a medicament for the treatment of mycobacterial diseases and a process for prepg. the claimed compds.



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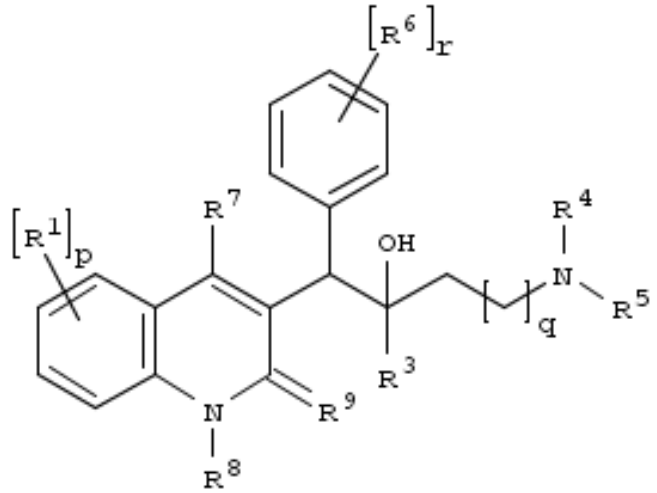

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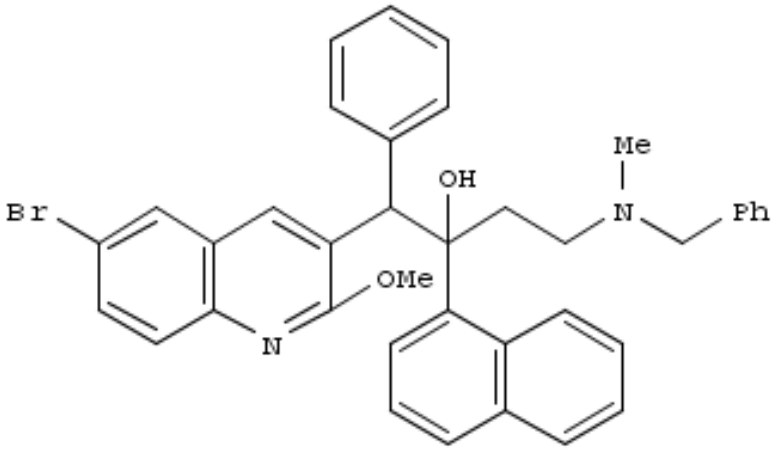


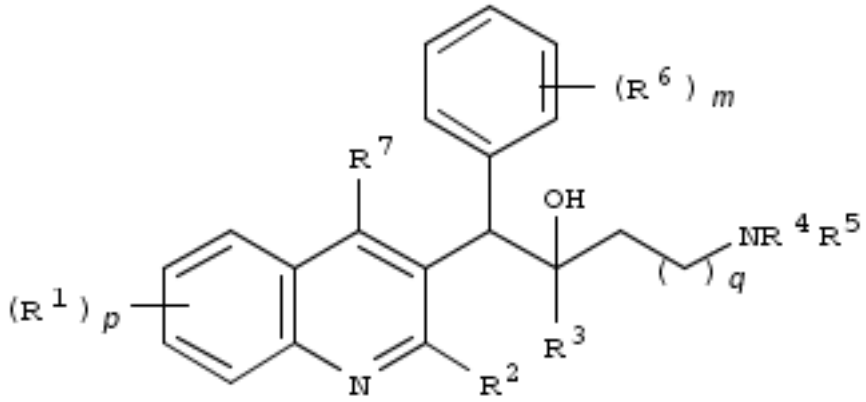
III

~12 Citings

4. Preparation of aminohydroxyaralkylquinolines for the treatment of drug resistant mycobacterial diseases

By Andries, Koenraad Jozef Lodewijk Marcel; Van Gestel, Jozef Frans Elisabetha
From PCT Int. Appl. (2005), WO 2005117875 A1 20051215, Language: English, Database: CAPLUS

Use of title compds. [I, II; R^1 = H, halo, haloalkyl, cyano, OH, aryl, heterocyclyl, alkyl, alkoxy, alkylthio, alkoxyalkyl, etc.; p = 1-4; R^2 = H, OH, SH, alkoxy, alkylthio, alkylamino, etc.; R^3 = alkyl, aryl, heterocyclyl, aralkyl, heterocyclylalkyl; q = 0-4; R^4, R^5 = H, alkyl, $PhCH_2$; R^4R^5N = (substituted) pyrrolidinyl, imidazolyl, morpholinyl, thiomorpholinyl, pyrazinyl, etc.; R^6 = H, halo, haloalkyl, OH, aryl, alkyl, alkoxy, alkylthio, aralkyl, etc.; 2 vicinal R^6 = CH:CHCH:CH; m = 1-5; R^7 = H, alkyl, aryl, heterocyclyl; R^8 = H, alkyl; R^9 = O; R^8R^9 = NCH:CH] for prepn. of a medicament for treatment of an infection with a drug resistant Mycobacterium strain is claimed. Title compds. showed min. inhibitory concns. of 0.06-0.12 mg/L against isoniazid-resistant M. tuberculosis.



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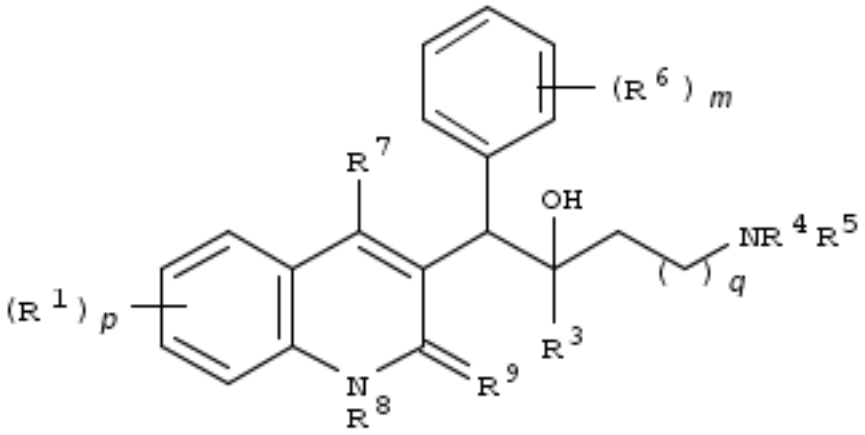


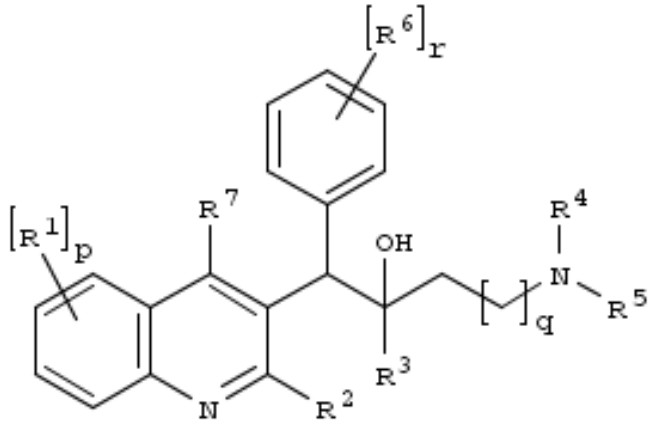
II

~25 Citings

5. Preparation of quinoline derivatives and their use as mycobacterial inhibitors

By Van Gestel, Jozef Frans Elisabetha; Guillemont, Jerome Emile Georges; Venet, Marc Gaston; Poignet, Herve Jean Joseph; Decrane, Laurence Francoise Bernadette; Vernier, Daniel F. J.; Odds, Frank Christopher
From U.S. Pat. Appl. Publ. (2005), US 20050148581 A1 20050707, Language: English, Database: CAPLUS

The title compds. [I or II; R^1 = H, halo, haloalkyl, CN, etc.; p = 0-4; R^2 = H, OH, thio, alkoxy, etc.; R^3 = alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl; q = 0-4; R^4, R^5 = H, alkyl, CH_2Ph; or NR^4R^5 = pyrrolidinyl, imidazolyl, triazolyl, etc.; R^6 = H, halo, haloalkyl, etc.; or two vicinal R^6 may be taken together to form CH:CHCH:CH; r = 0-5; R^7 = H, alkyl, aryl, heteroaryl; R^8 = H, alkyl; R^9 = oxo; or R^8 and R^9 together form NCH:CH] which are useful for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as Mycobacterium tuberculosis, M. bovis, M. avium and M. marinum, were prepd. In particular, compds. are claimed in which, independently from each other, R^1 = Br, p = 1, R^2 = alkyloxy, R^3 = (un)substituted naphthyl or Ph, q = 1, R^4 and R^5 each independently = H, Me or Et, R^6 = H, r = 0-1 and R^7 = H. E.g., a multi-step synthesis of III which showed MIC of 0.34 μg/mL and pIC_{50} of 8.5 against M. tuberculosis and M. smegmatis, resp., was given. Also claimed is a compn. comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amt. of the claimed compds. I, the use of the claimed compds. or compns. for the manuf. of a medicament for the treatment of mycobacterial diseases and a process for prepg. the claimed compds.



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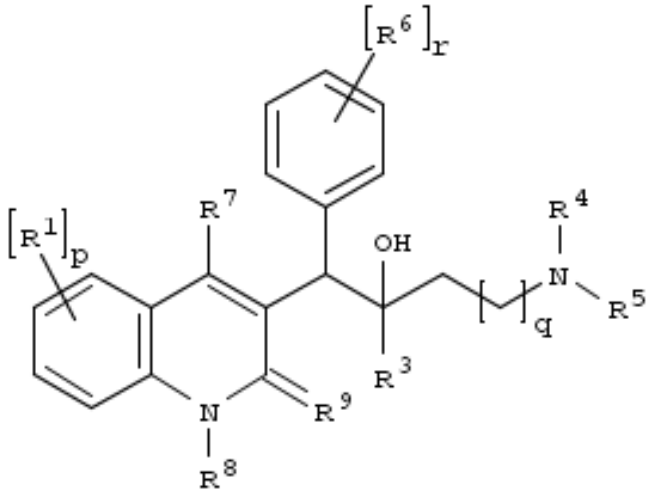

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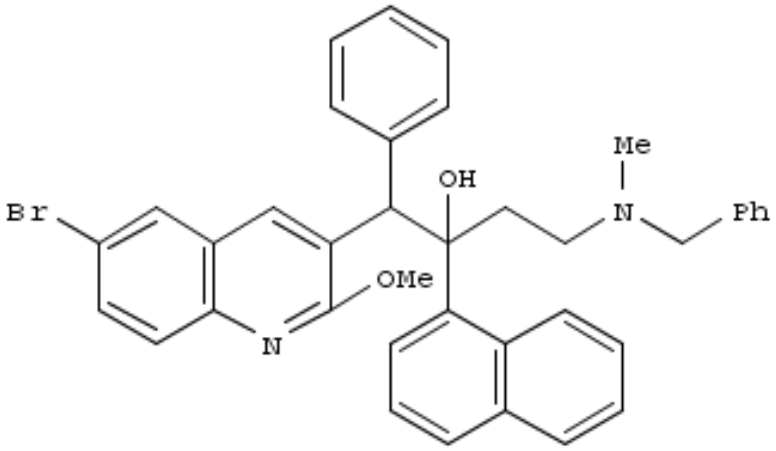


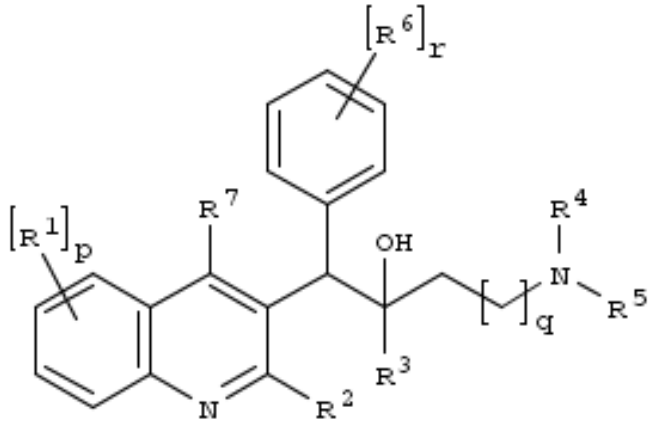
III

~12 Citings

6. Preparation of quinoline derivatives and their use as mycobacterial inhibitors

By Guillemont, Jerome Emile Georges; Van Gestel, Jozef Frans Elisabetha; Venet, Marc Gaston; Poignet, Herve Jean Joseph; Decrane, Laurence Francoise Bernadette; Vernier, Daniel F. J.
From PCT Int. Appl. (2004), WO 2004011436 A1 20040205, Language: English, Database: CAPLUS

The title compds. [I or II; R^1 = H, halo, haloalkyl, CN, etc.; p = 0-4; R^2 = H, OH, thio, alkoxy, etc.; R^3 = alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl; q = 0-4; R^4, R^5 = H, alkyl, CH_2Ph; or NR^4R^5 = pyrrolidinyl, imidazolyl, triazolyl, etc.; R^6 = H, halo, haloalkyl, etc.; or two vicinal R^6 may be taken together to form C:CC:C; r = 0-5; R^7 = H, alkyl, aryl, heteroaryl; R^8 = H, alkyl; R^9 = oxo; or R^8 and R^9 together form NCH:CH] which are useful for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as Mycobacterium tuberculosis, M. bovis, M. avium and M. marinum, were prepd. In particular, compds. are claimed in which, independently from each other, R^1 = Br, p = 1, R^2 = alkyloxy, R^3 = (un)substituted naphthyl or Ph, q = 1, R^4 and R^5 each independently = H, Me or Et, R^6 = H, r = 0-1 and R^7 = H. E.g., a multi-step synthesis of III which showed MIC of 0.34 μg/mL and pIC_{50} of 8.5 against M. tuberculosis and M. smegmatis, resp., was given. Also claimed is a compn. comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amt. of the claimed compds. I, the use of the claimed compds. or compns. for the manuf. of a medicament for the treatment of mycobacterial diseases and a process for prepg. the claimed compds.



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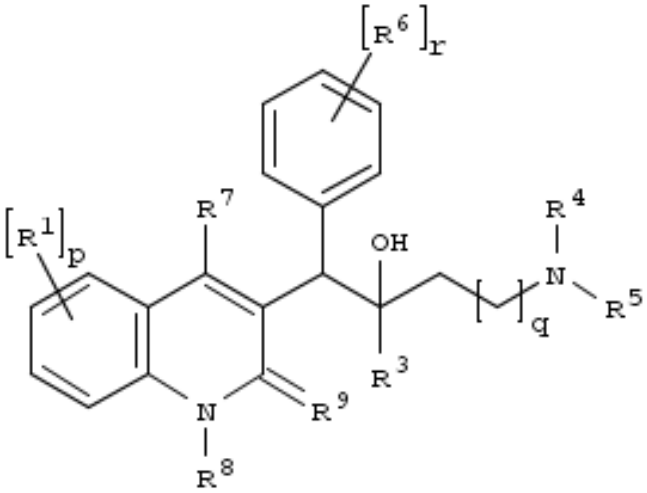

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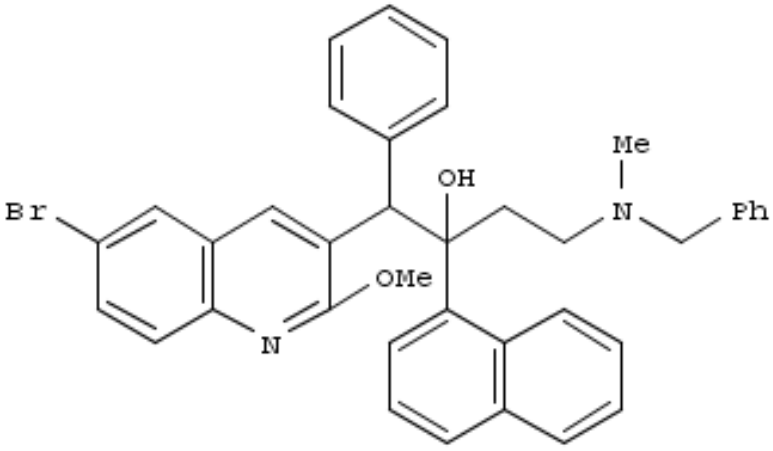


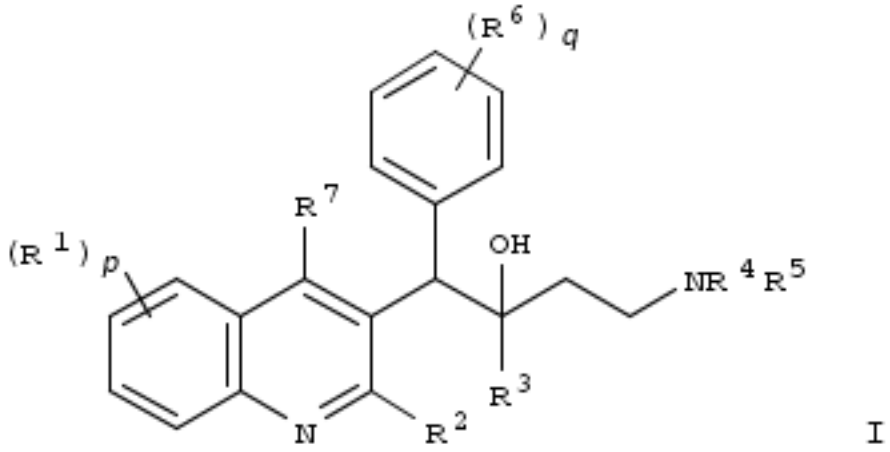
III

~58 Citings

1. Preparation of aminohydroxyphenylbutylquinolines as antibacterials.

By Andries, Koenraad Jozef Lodewijk Marcel; Koul, Anil; Guillemont, Jerome Emile Georges; Pasquier, Elisabeth Therese Jeanne; Lancois, David Francis Alain
From PCT Int. Appl. (2006), WO 2006131519 A1 20061214, Language: English, Database: CAPLUS

Use of title compds. [I; R^1 = H, halo, polyhaloalkyl, alkyl, hydroxyalkyl, alkoxy, Ar, Het; p, q = 1, 2; R^2 = alkoxy, alkoxyalkoxy, alkylthio; R^3 = alkyl, Ar, Het, Het1; R^4, R^5 = H, alkyl, benzyl; R^4R^5N = (substituted) pyrrolidinyl, pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, imidazolinyl, pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, piperidinyl, pyridinyl, piperazinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl, thiomorpholinyl; R^6 = H, halo, polyhaloalkyl, alkyl, alkoxy, alkylthio; 2 vicinal R^6 may = CH:CHCH:CH; R^7 = H, alkyl, Ar, Het, Het1; Ar = (substituted) Ph, naphthyl, acenaphthyl, 1,2-dihydroacenaphthyl, tetrahydronaphthyl; Het = (substituted) piperidyl, pyrrolyl, N-phenoxypiperidyl, pyrazolyl, triazolyl, imidazolyl, furyl, pyridyl, pyrimidyl, pyrazinyl, etc.; Het1 = (substituted) quinolyl, quinoxalinyl, indolyl, benzimidazolyl, benzofuryl, benzothienyl, 2,3-dihydrobenzodioxinyl, etc.; with provisos], for manuf. of a medicament for treatment of bacterial infection is claimed. Thus, a diastereomer of title compd. (II) (prepn. outlined) showed an IC_{90} = 10.8 μg/mL against Streptococcus mutans ATCC33402.



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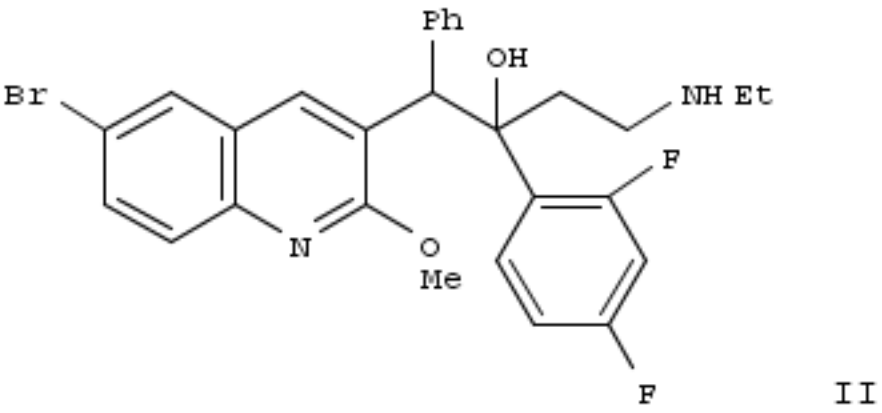


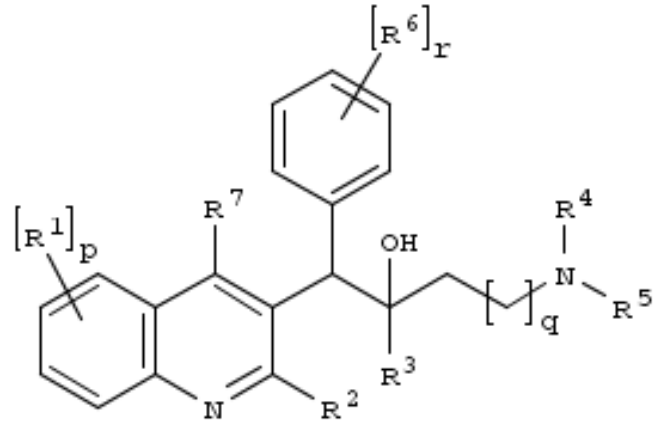
II

~10 Citings

2. Preparation of quinoline derivatives and their use as mycobacterial inhibitors

By Koul, Anil; Andries, Koenraad Jozef Lodewijk Marcel
From Can. Pat. Appl. (2006), CA 2529265 A1 20060624, Language: English, Database: CAPLUS

The title compds. [I or II; R^1 = H, halo, haloalkyl, CN, etc.; p = 0-4; R^2 = H, OH, thio, alkoxy, etc.; R^3 = alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl; q = 0-4; R^4, R^5 = H, alkyl, CH_2Ph; or NR^4R^5 = pyrrolidinyl, imidazolyl, triazolyl, etc.; R^6 = H, halo, haloalkyl, etc.; or two vicinal R^6 may be taken together to form CH:CHCH:CH; r = 0-5; R^7 = H, alkyl, aryl, heteroaryl; R^8 = H, alkyl; R^9 = oxo; or R^8 and R^9 together form NCH:CH] which are useful for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as Mycobacterium tuberculosis, M. bovis, M. avium and M. marinum, were prepd. In particular, compds. are claimed in which, independently from each other, R^1 = Br, p = 1, R^2 = alkyloxy, R^3 = (un)substituted naphthyl or Ph, q = 1, R^4 and R^5 each independently = H, Me or Et, R^6 = H, r = 0-1 and R^7 = H. E.g., a multi-step synthesis of III which showed MIC of 0.34 μg/mL and pIC_{50} of 8.5 against M. tuberculosis and M. smegmatis, resp., was given. Also claimed is a compn. comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amt. of the claimed compds. I, the use of the claimed compds. or compns. for the manuf. of a medicament for the treatment of mycobacterial diseases and a process for prepg. the claimed compds.



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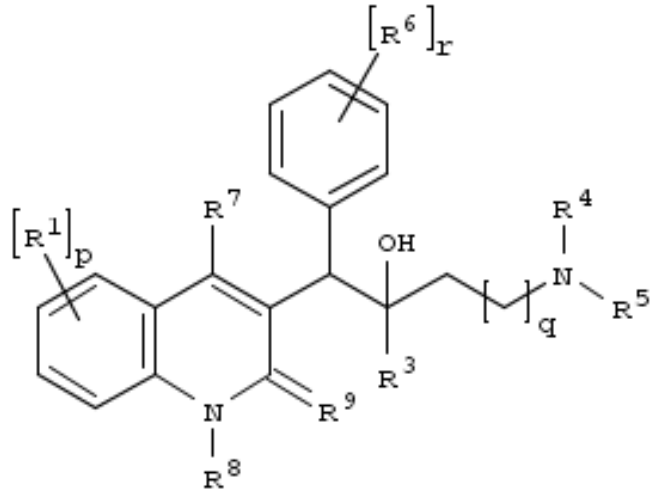

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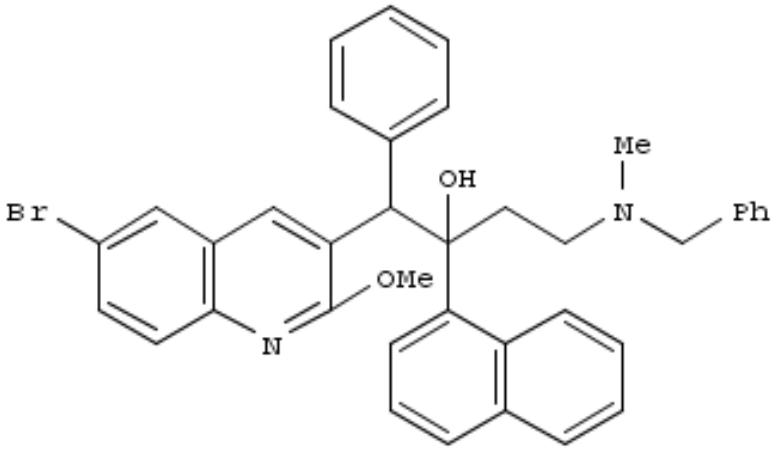


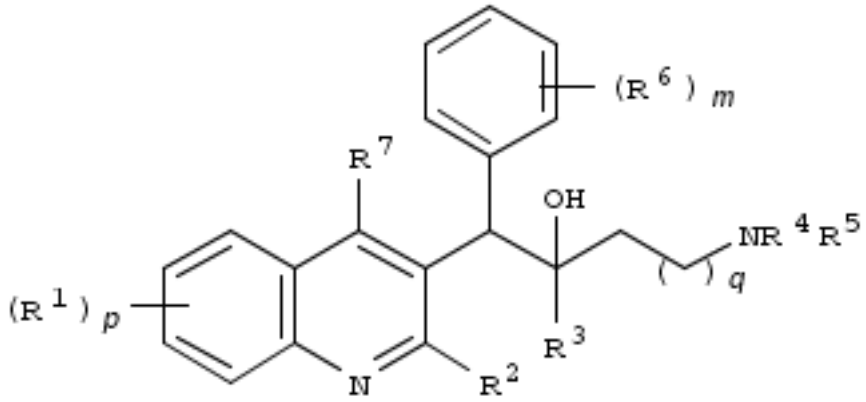
III

~12 Citings

3. Preparation of aminohydroxyaralkylquinolines for the treatment of drug resistant mycobacterial diseases

By Andries, Koenraad Jozef Lodewijk Marcel; Van Gestel, Jozef Frans Elisabetha
From PCT Int. Appl. (2005), WO 2005117875 A1 20051215, Language: English, Database: CAPLUS

Use of title compds. [I, II; R^1 = H, halo, haloalkyl, cyano, OH, aryl, heterocyclyl, alkyl, alkoxy, alkylthio, alkoxyalkyl, etc.; p = 1-4; R^2 = H, OH, SH, alkoxy, alkylthio, alkylamino, etc.; R^3 = alkyl, aryl, heterocyclyl, aralkyl, heterocyclylalkyl; q = 0-4; R^4, R^5 = H, alkyl, $PhCH_2$; R^4R^5N = (substituted) pyrrolidinyl, imidazolyl, morpholinyl, thiomorpholinyl, pyrazinyl, etc.; R^6 = H, halo, haloalkyl, OH, aryl, alkyl, alkoxy, alkylthio, aralkyl, etc.; 2 vicinal R^6 = CH:CHCH:CH; m = 1-5; R^7 = H, alkyl, aryl, heterocyclyl; R^8 = H, alkyl; R^9 = O; R^8R^9 = NCH:CH] for prepn. of a medicament for treatment of an infection with a drug resistant Mycobacterium strain is claimed. Title compds. showed min. inhibitory concns. of 0.06-0.12 mg/L against isoniazid-resistant M. tuberculosis.



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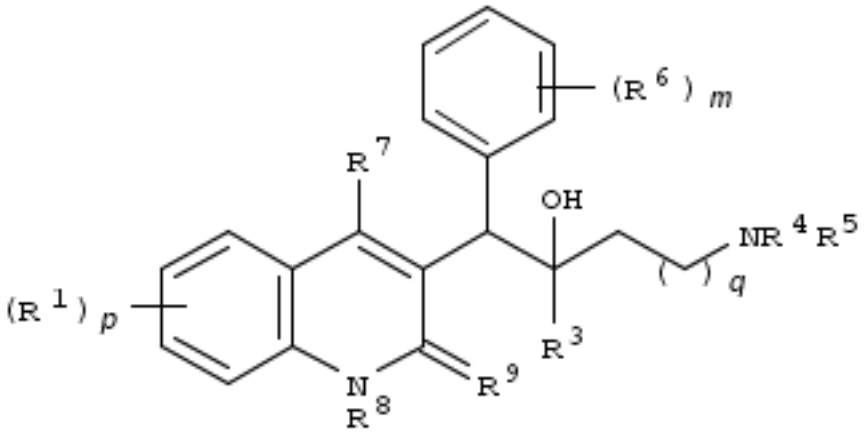


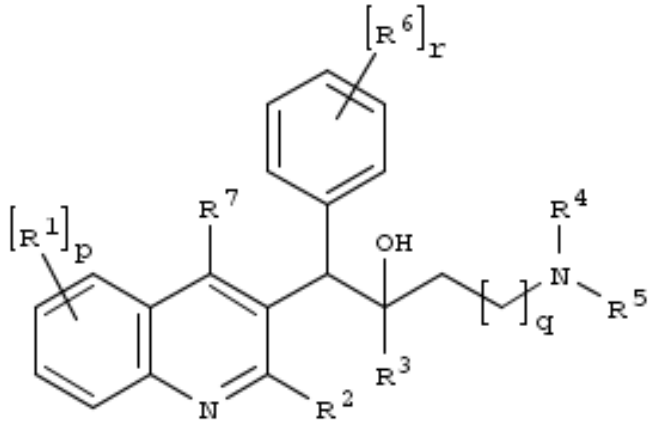
II

~25 Citings

4. Preparation of quinoline derivatives and their use as mycobacterial inhibitors

By Van Gestel, Jozef Frans Elisabetha; Guillemont, Jerome Emile Georges; Venet, Marc Gaston; Poignet, Herve Jean Joseph; Decrane, Laurence Francoise Bernadette; Vernier, Daniel F. J.; Odds, Frank Christopher
From U.S. Pat. Appl. Publ. (2005), US 20050148581 A1 20050707, Language: English, Database: CAPLUS

The title compds. [I or II; R^1 = H, halo, haloalkyl, CN, etc.; p = 0-4; R^2 = H, OH, thio, alkoxy, etc.; R^3 = alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl; q = 0-4; R^4, R^5 = H, alkyl, CH_2Ph; or NR^4R^5 = pyrrolidinyl, imidazolyl, triazolyl, etc.; R^6 = H, halo, haloalkyl, etc.; or two vicinal R^6 may be taken together to form CH:CHCH:CH; r = 0-5; R^7 = H, alkyl, aryl, heteroaryl; R^8 = H, alkyl; R^9 = oxo; or R^8 and R^9 together form NCH:CH] which are useful for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as Mycobacterium tuberculosis, M. bovis, M. avium and M. marinum, were prepd. In particular, compds. are claimed in which, independently from each other, R^1 = Br, p = 1, R^2 = alkyloxy, R^3 = (un)substituted naphthyl or Ph, q = 1, R^4 and R^5 each independently = H, Me or Et, R^6 = H, r = 0-1 and R^7 = H. E.g., a multi-step synthesis of III which showed MIC of 0.34 μg/mL and pIC_{50} of 8.5 against M. tuberculosis and M. smegmatis, resp., was given. Also claimed is a compn. comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amt. of the claimed compds. I, the use of the claimed compds. or compns. for the manuf. of a medicament for the treatment of mycobacterial diseases and a process for prepg. the claimed compds.



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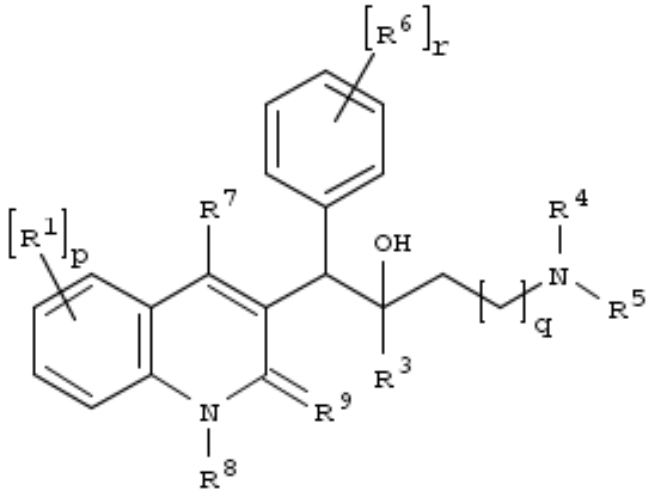

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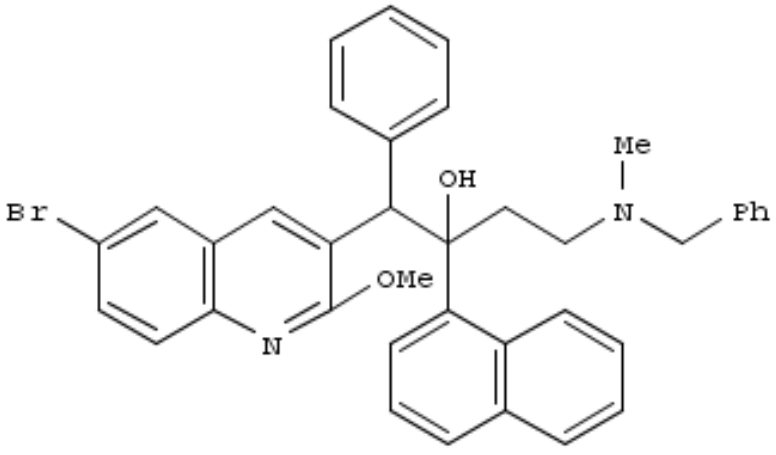


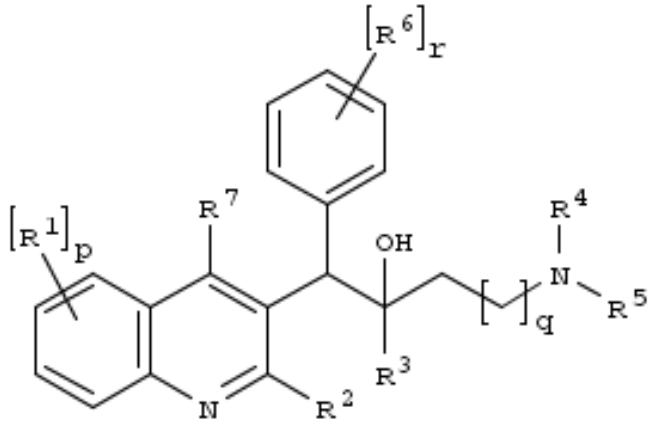
III

~12 Citings

5. Preparation of quinoline derivatives and their use as mycobacterial inhibitors

By Guillemont, Jerome Emile Georges; Van Gestel, Jozef Frans Elisabetha; Venet, Marc Gaston; Poignet, Herve Jean Joseph; Decrane, Laurence Francoise Bernadette; Vernier, Daniel F. J.
From PCT Int. Appl. (2004), WO 2004011436 A1 20040205, Language: English, Database: CAPLUS

The title compds. [I or II; R^1 = H, halo, haloalkyl, CN, etc.; p = 0-4; R^2 = H, OH, thio, alkoxy, etc.; R^3 = alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl; q = 0-4; R^4, R^5 = H, alkyl, CH_2Ph; or NR^4R^5 = pyrrolidinyl, imidazolyl, triazolyl, etc.; R^6 = H, halo, haloalkyl, etc.; or two vicinal R^6 may be taken together to form C:CC:C; r = 0-5; R^7 = H, alkyl, aryl, heteroaryl; R^8 = H, alkyl; R^9 = oxo; or R^8 and R^9 together form NCH:CH] which are useful for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as Mycobacterium tuberculosis, M. bovis, M. avium and M. marinum, were prepd. In particular, compds. are claimed in which, independently from each other, R^1 = Br, p = 1, R^2 = alkyloxy, R^3 = (un)substituted naphthyl or Ph, q = 1, R^4 and R^5 each independently = H, Me or Et, R^6 = H, r = 0-1 and R^7 = H. E.g., a multi-step synthesis of III which showed MIC of 0.34 μg/mL and pIC_{50} of 8.5 against M. tuberculosis and M. smegmatis, resp., was given. Also claimed is a compn. comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amt. of the claimed compds. I, the use of the claimed compds. or compns. for the manuf. of a medicament for the treatment of mycobacterial diseases and a process for prepg. the claimed compds.



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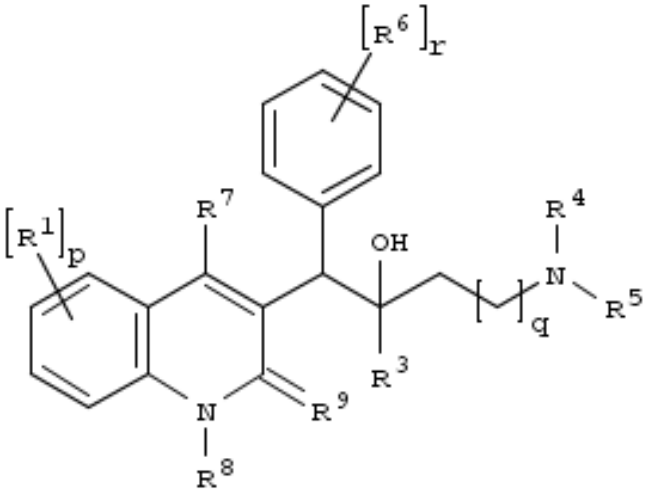

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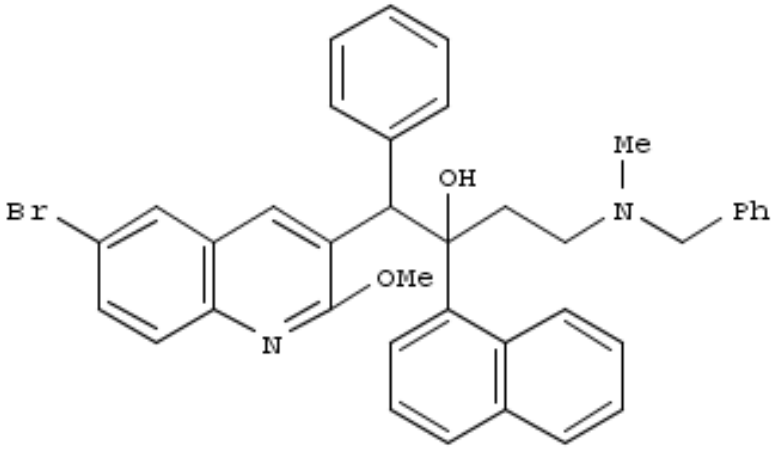


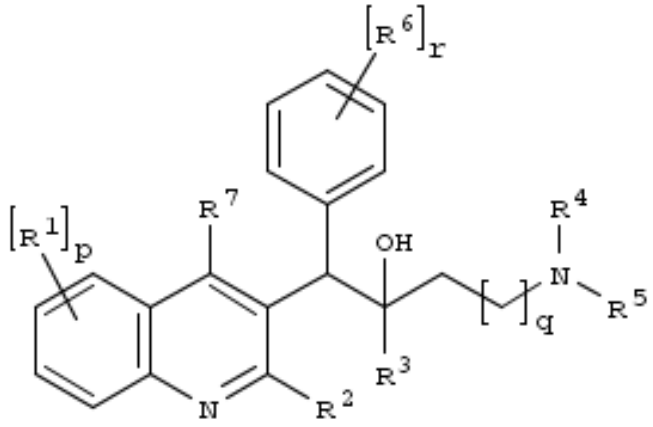
III

~58 Citings

1. Preparation of quinoline derivatives and their use as mycobacterial inhibitors

By Koul, Anil; Andries, Koenraad Jozef Lodewijk Marcel
From Can. Pat. Appl. (2006), CA 2529265 A1 20060624, Language: English, Database: CAPLUS

The title compds. [I or II; R^1 = H, halo, haloalkyl, CN, etc.; p = 0-4; R^2 = H, OH, thio, alkoxy, etc.; R^3 = alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl; q = 0-4; R^4, R^5 = H, alkyl, CH_2Ph; or NR^4R^5 = pyrrolidinyl, imidazolyl, triazolyl, etc.; R^6 = H, halo, haloalkyl, etc.; or two vicinal R^6 may be taken together to form CH:CHCH:CH; r = 0-5; R^7 = H, alkyl, aryl, heteroaryl; R^8 = H, alkyl; R^9 = oxo; or R^8 and R^9 together form NCH:CH] which are useful for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as Mycobacterium tuberculosis, M. bovis, M. avium and M. marinum, were prepd. In particular, compds. are claimed in which, independently from each other, R^1 = Br, p = 1, R^2 = alkyloxy, R^3 = (un)substituted naphthyl or Ph, q = 1, R^4 and R^5 each independently = H, Me or Et, R^6 = H, r = 0-1 and R^7 = H. E.g., a multi-step synthesis of III which showed MIC of 0.34 μg/mL and pIC_{50} of 8.5 against M. tuberculosis and M. smegmatis, resp., was given. Also claimed is a compn. comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amt. of the claimed compds. I, the use of the claimed compds. or compns. for the manuf. of a medicament for the treatment of mycobacterial diseases and a process for prepg. the claimed compds.



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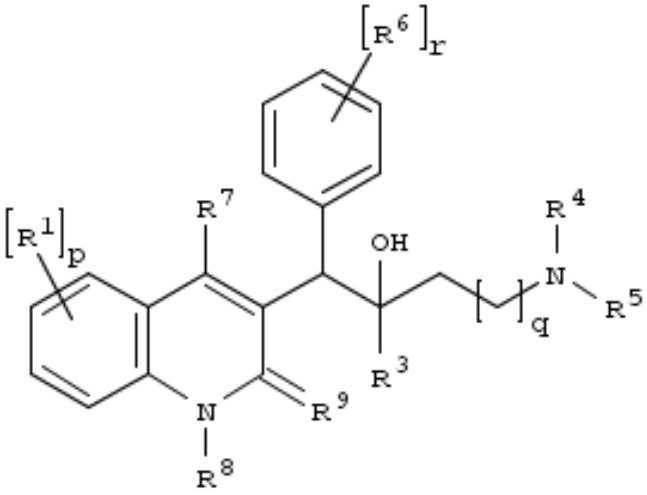

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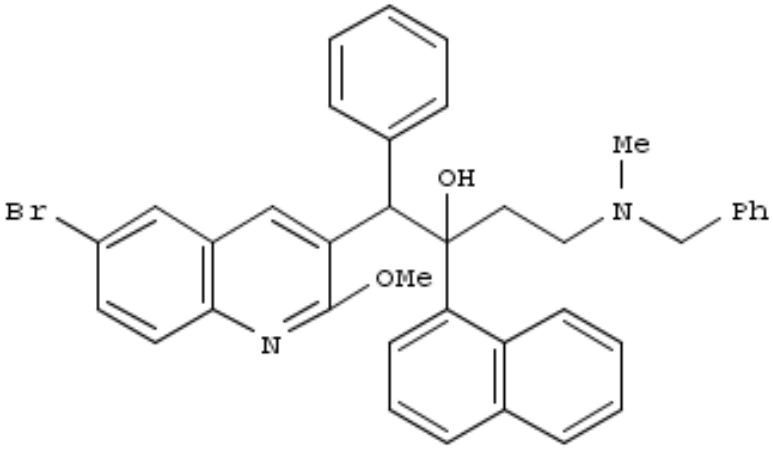


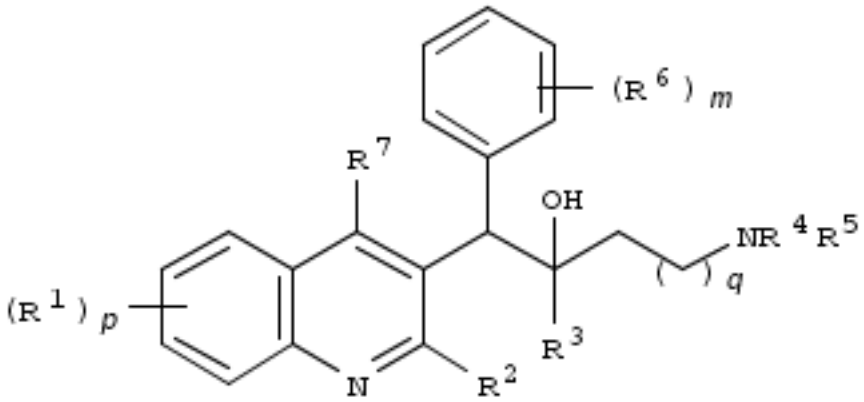
III

~12 Citings

2. Preparation of aminohydroxyaralkylquinolines for the treatment of drug resistant mycobacterial diseases

By Andries, Koenraad Jozef Lodewijk Marcel; Van Gestel, Jozef Frans Elisabetha
From PCT Int. Appl. (2005), WO 2005117875 A1 20051215, Language: English, Database: CAPLUS

Use of title compds. [I, II; R^1 = H, halo, haloalkyl, cyano, OH, aryl, heterocyclyl, alkyl, alkoxy, alkylthio, alkoxyalkyl, etc.; p = 1-4; R^2 = H, OH, SH, alkoxy, alkylthio, alkylamino, etc.; R^3 = alkyl, aryl, heterocyclyl, aralkyl, heterocyclylalkyl; q = 0-4; R^4, R^5 = H, alkyl, $PhCH_2$; R^4R^5N = (substituted) pyrrolidinyl, imidazolyl, morpholinyl, thiomorpholinyl, pyrazinyl, etc.; R^6 = H, halo, haloalkyl, OH, aryl, alkyl, alkoxy, alkylthio, aralkyl, etc.; 2 vicinal R^6 = CH:CHCH:CH; m = 1-5; R^7 = H, alkyl, aryl, heterocyclyl; R^8 = H, alkyl; R^9 = O; R^8R^9 = NCH:CH] for prepn. of a medicament for treatment of an infection with a drug resistant Mycobacterium strain is claimed. Title compds. showed min. inhibitory concns. of 0.06-0.12 mg/L against isoniazid-resistant M. tuberculosis.



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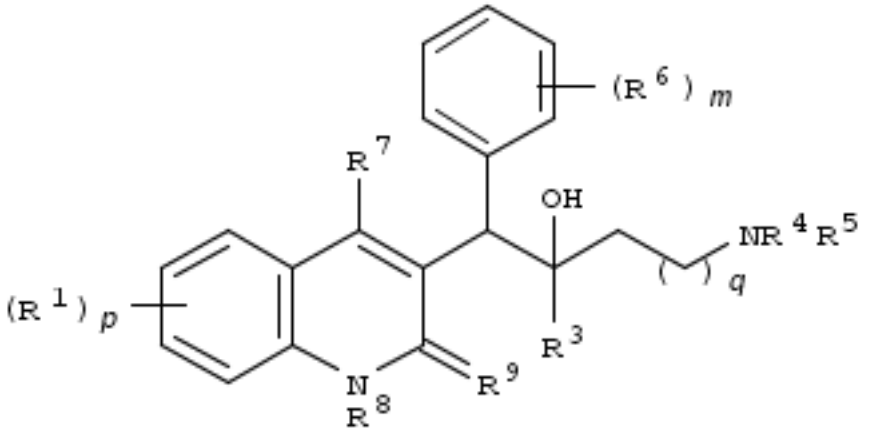


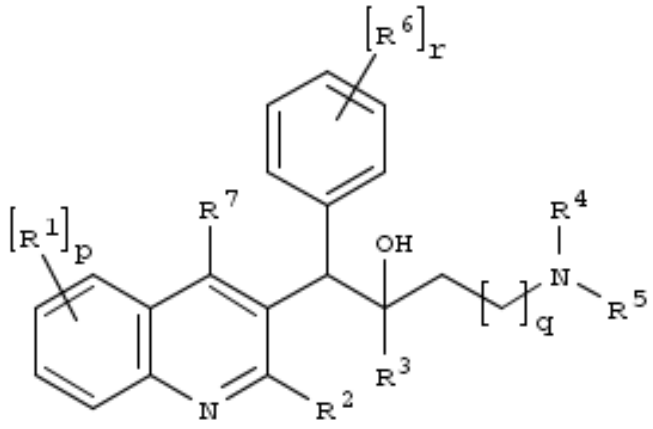
II

~25 Citings

3. Preparation of quinoline derivatives and their use as mycobacterial inhibitors

By Van Gestel, Jozef Frans Elisabetha; Guillemont, Jerome Emile Georges; Venet, Marc Gaston; Poignet, Herve Jean Joseph; Decrane, Laurence Francoise Bernadette; Vernier, Daniel F. J.; Odds, Frank Christopher
From U.S. Pat. Appl. Publ. (2005), US 20050148581 A1 20050707, Language: English, Database: CAPLUS

The title compds. [I or II; R^1 = H, halo, haloalkyl, CN, etc.; p = 0-4; R^2 = H, OH, thio, alkoxy, etc.; R^3 = alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl; q = 0-4; R^4, R^5 = H, alkyl, CH_2Ph; or NR^4R^5 = pyrrolidinyl, imidazolyl, triazolyl, etc.; R^6 = H, halo, haloalkyl, etc.; or two vicinal R^6 may be taken together to form CH:CHCH:CH; r = 0-5; R^7 = H, alkyl, aryl, heteroaryl; R^8 = H, alkyl; R^9 = oxo; or R^8 and R^9 together form NCH:CH] which are useful for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as Mycobacterium tuberculosis, M. bovis, M. avium and M. marinum, were prepd. In particular, compds. are claimed in which, independently from each other, R^1 = Br, p = 1, R^2 = alkyloxy, R^3 = (un)substituted naphthyl or Ph, q = 1, R^4 and R^5 each independently = H, Me or Et, R^6 = H, r = 0-1 and R^7 = H. E.g., a multi-step synthesis of III which showed MIC of 0.34 μg/mL and pIC_{50} of 8.5 against M. tuberculosis and M. smegmatis, resp., was given. Also claimed is a compn. comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amt. of the claimed compds. I, the use of the claimed compds. or compns. for the manuf. of a medicament for the treatment of mycobacterial diseases and a process for prepg. the claimed compds.



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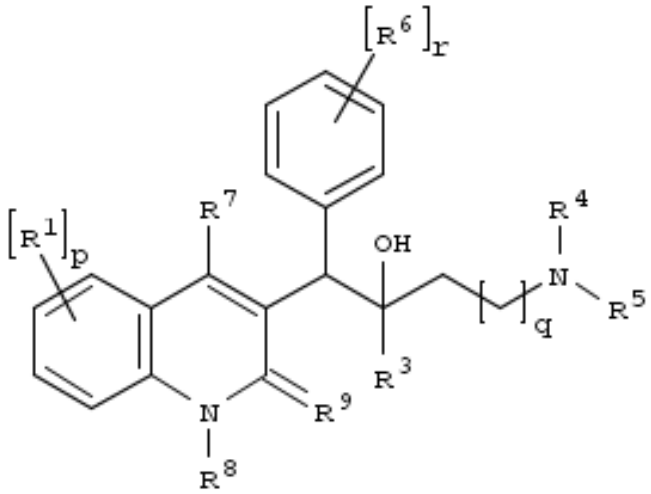

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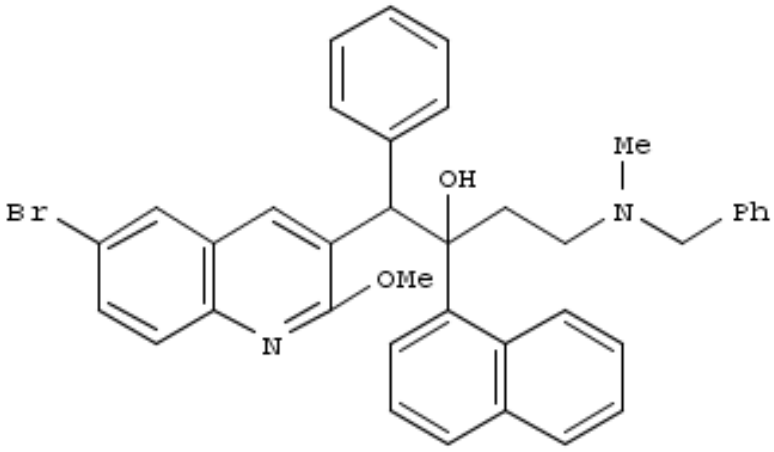


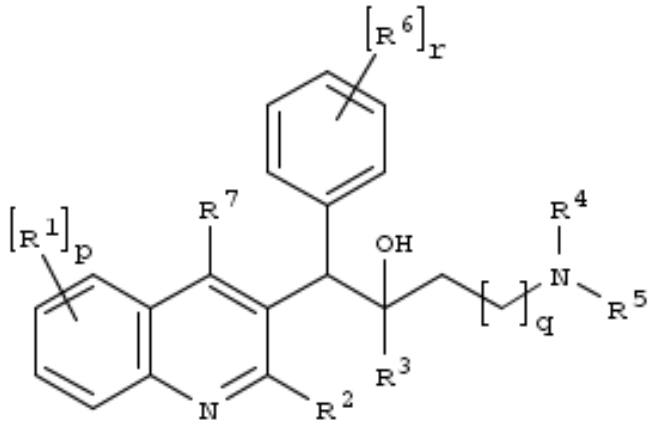
III

~12 Citings

4. Preparation of quinoline derivatives and their use as mycobacterial inhibitors

By Guillemont, Jerome Emile Georges; Van Gestel, Jozef Frans Elisabetha; Venet, Marc Gaston; Poignet, Herve Jean Joseph; Decrane, Laurence Francoise Bernadette; Vernier, Daniel F. J.
From PCT Int. Appl. (2004), WO 2004011436 A1 20040205, Language: English, Database: CAPLUS

The title compds. [I or II; R^1 = H, halo, haloalkyl, CN, etc.; p = 0-4; R^2 = H, OH, thio, alkoxy, etc.; R^3 = alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl; q = 0-4; R^4, R^5 = H, alkyl, CH_2Ph; or NR^4R^5 = pyrrolidinyl, imidazolyl, triazolyl, etc.; R^6 = H, halo, haloalkyl, etc.; or two vicinal R^6 may be taken together to form C:CC:C; r = 0-5; R^7 = H, alkyl, aryl, heteroaryl; R^8 = H, alkyl; R^9 = oxo; or R^8 and R^9 together form NCH:CH] which are useful for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as Mycobacterium tuberculosis, M. bovis, M. avium and M. marinum, were prepd. In particular, compds. are claimed in which, independently from each other, R^1 = Br, p = 1, R^2 = alkyloxy, R^3 = (un)substituted naphthyl or Ph, q = 1, R^4 and R^5 each independently = H, Me or Et, R^6 = H, r = 0-1 and R^7 = H. E.g., a multi-step synthesis of III which showed MIC of 0.34 μg/mL and pIC_{50} of 8.5 against M. tuberculosis and M. smegmatis, resp., was given. Also claimed is a compn. comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amt. of the claimed compds. I, the use of the claimed compds. or compns. for the manuf. of a medicament for the treatment of mycobacterial diseases and a process for prepg. the claimed compds.



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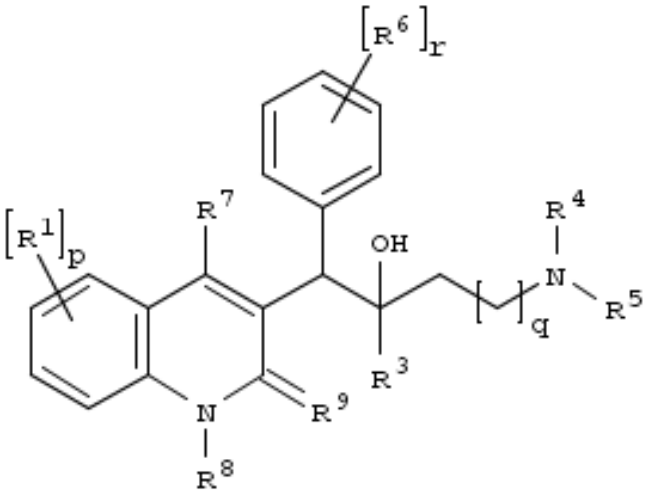

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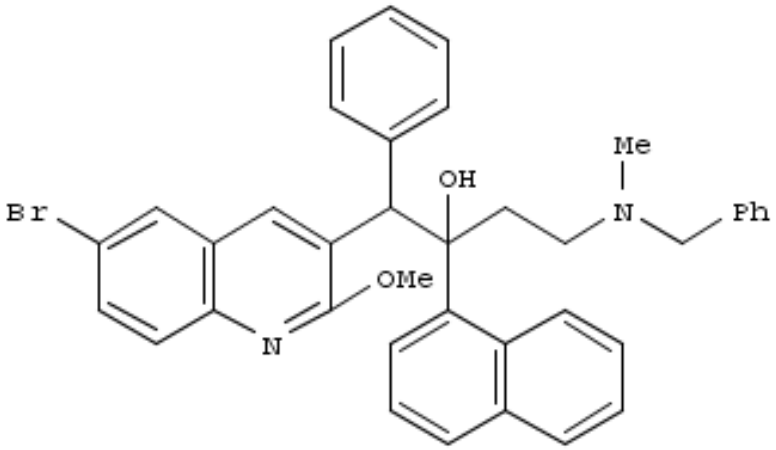


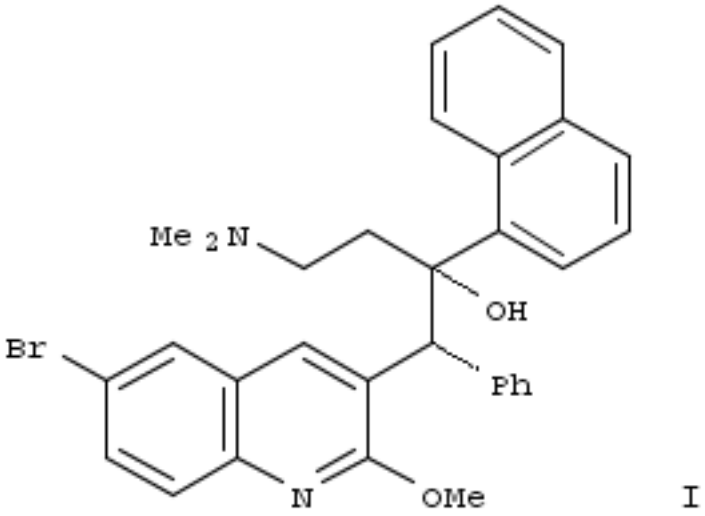
III

~58 Citings

1. Rational drug design based synthesis of novel arylquinolines as anti-tuberculosis agents

By Jain, Puneet P.; Degani, Mariam S.; Raju, Archana; Ray, Muktikanta; Rajan, M. G. R.
From Bioorganic & Medicinal Chemistry Letters (2013), 23(22), 6097-6105. Language: English, Database: CAPLUS, DOI:10.1016/j.bmcl.2013.09.027

A series of novel arylquinoline derivs. was designed retaining significant pharmacophoric features and three dimensional geometry of bedaquiline (I). In silico ADME study was performed to assess drug likeness and toxicity profiles of the designed mols. The compds. were evaluated for activity against Mycobacterium tuberculosis $H_{37}Rv$ using Resazurin Microtitre Assay (REMA) plate method and cytotoxicity in VERO C1008 cell line. Several of the synthesized compds. exhibited good antituberculosis activity and selectivity, esp. compds., II (R = H) (MIC: 5.18 μM and MIC/CC_{50}: 152.86) and II (R = Cl) (MIC: 5.59 μM and MIC/CC_{50}: 160.57). The study opens up a new platform for the development of arylquinoline based drugs for treating tuberculosis.



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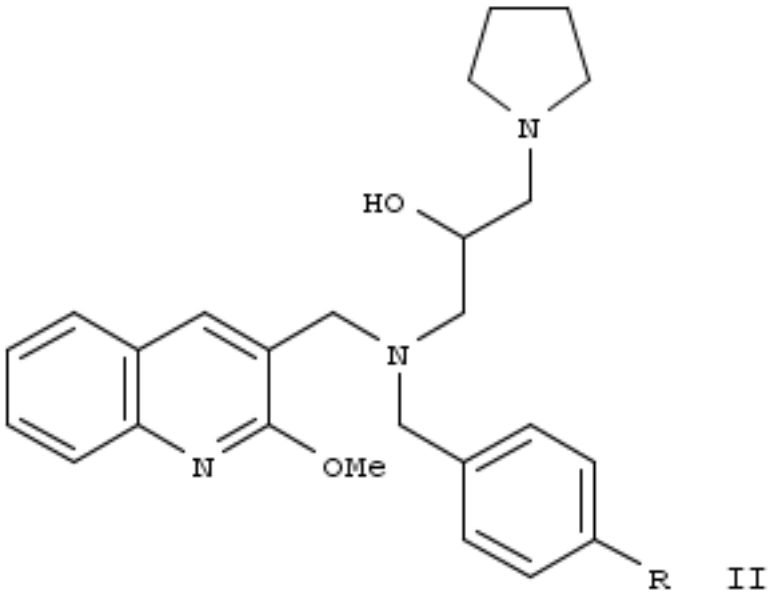

II

~18 Citings