Published in final edited form as:
ACS Comb Sci. 2012 September 10; 14(9): 496–502. doi:10.1021/co300068a.

Expedient Synthesis of Norbenzomorphan Library via Multicomponent Assembly Process Coupled with Ring-Closing Reactions

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Abstract

A 124 member norbenzomorphan library has been prepared utilizing a novel multicomponent assembly process (MCAP) followed by a variety of ring-closing reactions to generate norbenzomorphan scaffolds that were readily derivatized via a series of aryl halide cross-coupling and nitrogen functionalization reactions. Biological screening has revealed some novel activities that have not been previously associated with this class of compounds.

Keywords

Combinatorial chemistry; norbenzomorphan; multicomponent assembly process; Heck reaction; cross-coupling reactions

INTRODUCTION

The identification of novel, biologically active molecules is an integral part of programs that are directed toward drug discovery and development of molecular tools that probe biochemical and cellular function. To this end, the high-throughput screening (HTS) of privileged scaffold-based compound libraries has been an effective strategy for obtaining `hits' across a broad range of unrelated biological targets.[1] Once the `hit' compound's identity has been confirmed, it is then subjected to sequential rounds of optimization for specificity and potency by manipulation of appended functional groups, substituents, and ring substitution patterns. Since privileged structures are known to exhibit `drug-like' characteristics that include good absorption, membrane permeability, and oral bioavailability,[2] chemical libraries based upon these frameworks may have reduced downstream attrition rates making them well-suited for `lead' generation in drug discovery programs.

The 7-methoxy-2-methylnorbenzomorphan (**3**) was first synthesized in the 1960's during a campaign to discover analgesics more potent than benzomorphan (**2**), a fundamental structural subunit found in morphine (**1**) and related opiates (Figure 1).[3] A number of members from this new class of heterocycles were identified, including **3**, that exhibited analgesic activity in mouse models that was comparable to that of codeine, thus supporting the hypothesis that preparing compounds of this molecular class could lead to the

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SUPPORTING INFORMATION Experimental procedures, full characterization data, and tabulated Lipinski parameters for representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

development of novel antinociceptive agents. In a later effort to improve upon the acetylcholinesterase (AChE) inhibitory activity of (−)-physostigmine, a natural product with a wide range of clinical uses,[4] a series of norbenzomorphans sharing specific heteroatomic spatial relationships with the natural product were assayed.[5] These studies led to the identification of a novel class of norbenzomorphan AChE inhibitors, including **4**, that exhibited improved potency and reduced *in vivo* toxicity relative to (−)-physostigmine. It thus occurred to us that the low molecular weight of the norbenzomorphan scaffold, coupled with its promise as a biologically relevant molecular framework, made it an attractive platform for the construction of a library of novel compounds for use in HTS assays.

In order to access a set of diversely substituted norbenzomorphans, a synthetic approach to the azabicyclic skeleton that was both expedient and flexible in terms of the substitution pattern on the aromatic ring and the nitrogen atom was critically important. We elected to prepare scaffolds with aromatic chlorine atoms at various positions (**5**, Figure 1), because these would serve as functional handles to further derivatize the norbenzomorphan nucleus. The robust nature of the aryl chloride allowed it to be present in the starting material and throughout the scaffold construction sequence, yet it would readily participate in a variety of cross-coupling reactions at the desired stage.

We recently described a general approach to diversity oriented synthesis (DOS) that features a multicomponent assembly process (MCAP) followed by various ring forming reactions.[6] The inspiration for this strategy owed its origin to chemistry we had developed in the context of the synthesis of complex alkaloid natural products.[7] In the MCAP step of the sequence, three or more reactants are combined to give versatile intermediates, which are endowed with different functional groups that can be paired in a variety of ways to enable cyclizations by numerous ring closing reactions. This basic strategy for DOS has been recently applied to the rapid syntheses of novel benzoxazocines,[8] benzazocines, benzodiazepines,[9] and tetrahydroisoquinolines,[10] as well as isoindolinones,[11] tetrahydrobenzonaphtheridines, pyridazines and norbenzomorphans. We now report the application of this strategy to the preparation of a large set of diversely substituted norbenzomorphans based upon **5**; we also present select biological screening data that reveal useful activities not previously associated with this class of compounds.

RESULTS AND DISCUSSION

The requisite chloro-regioisomeric norbenzomorphans **18**{*1–3*} were readily prepared in four steps from the known benzaldehydes **6–8** (Scheme 1).[12] In the event, sequential treatment of an aldehyde with allylamine, CbzCl and allylzinc bromide provided the diene carbamates **9–11** in good overall yield.[11] These diene carbamates **9–11** underwent facile ring closing reactions with Grubbs II catalyst to render tetrahydropyridines **12–14**. Subsequent cyclization of **12–14** via an intramolecular Heck reaction, which was promoted under microwave irradiation, furnished the enecarbamates **15–17**, which were reduced under ionic conditions to give the chloro norbenzomorphan scaffolds **18**{*1–3*}.

With multigram quantities of the chloro norbenzomorphans **18**{*1–3*} in hand, we prepared a set of norbenzomorphan derivatives using cross-coupling reactions involving the aryl chloride moiety. Some preliminary screening of conditions was required in order to identify the ideal catalysts, ligands, and reaction parameters that would promote cross-couplings of the aryl chlorides with various amines and boronic acids to provide an assortment of substituted norbenzomorphans **20** with diverse electronic properties and substitution patterns (Scheme 2, Table 1, Figure 2). Under optimized conditions, aniline derivatives **20**{*1,1–2*}, **20**{*2,1–4*} and **20**{*3,2*} were obtained from all three chloro regioisomers **18**{*1–3*} through a Buchwald-Hartwig reaction by pre-mixing $Pd(OAc)_2$ and JohnPhos® prior to addition to the reaction mixture (Table 1).[13] When these heterocycles were coupled with piperazine, it was necessary to use an excess (5 equiv) of the diamine to suppress bis-arylation. In all other coupling reactions that involved the use of primary or secondary aliphatic amines as reaction partners, complete consumption of aryl chloride was observed with the use of a slight excess of amine.

A number of commonly-used palladium precatalysts such as $Pd(OAc)_2$, $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ did not promote Suzuki couplings with **18**{*1–3*}, but we eventually discovered that 5 mol% Pd(*t*-$Bu_3P)_2$ was highly effective as a catalyst, delivering a broad range of biaryl norbenzomorphans **20**{*1,5*}, **20**{*2,6–11*} and **20**{*3,6–8*} in generally good yields (Scheme 2, Table 1, Figure 2).[14] A variety of amines and boronic acids were coupled to all three chloro regioisomers **18**{*1–3*} to deliver a set of norbenzomorphans adorned with groups having diverse electronic properties and substitution patterns. It is noteworthy that biaryl norbenzomorphans represent a novel class of compounds whose biology has yet to be examined.

Having prepared a collection of diversely substituted amino and aryl norbenzomorphans **20**, attention was directed to derivatizing the nitrogen atom of the scaffold. We discovered that a known, but rarely utilized tactic to access benzylamines directly from benzyl carbamates,[15] was nicely suited to the rapid generation of a small set of benzylamines. In the event, benzyl carbamates **18** and **20** (Scheme 3, Table 2) were treated with TMSI followed by quenching under basic conditions to give tertiary amines **21**; no quaternization was ever observed from the one-pot deprotection/benzylation reaction.

Functionalization of the protected nitrogen atom served as another means to diversify the norbenzomorphans. For example, carbamates **18** and **20** were readily converted to secondary amines by the action of TMSI or Pd(0) and hydrogen (Scheme 4, Table 3). When using TMSI, it was essential to quench the reaction with acid to avoid forming the tertiary benzylamine. Interestingly, Cbz removal under hydrogenolysis conditions with Pd(0) and hydrogen worked well with only a few substrates (Table 3, Entries 6–8); uncharacterized mixtures of compounds were obtained from other starting materials such as **20**{*2,2*} and **20**{*2,6*}.

With the free amines **22** and **23** in hand, a series of *N*-functionalization reactions were conducted to generate libraries of tertiary amines **25** and **26**, amides **27** and **28**, sulfonamides **29** and **30**, carbamates **31** and **32**, thioureas **33** and **34**, β-amino esters **35** and a β-amino cyanide **36** (Scheme 4, Table 4, Figure 3). Generally, the *N*-functionalizations of **22** and **23** were performed using a two-fold excess of commercially-available reagents to ensure complete consumption of the starting amine. Both aromatic and aliphatic reagents were employed in diversification reactions to give norbenzomorphan derivatives bearing substituents having a broad spectrum of electronic properties, which will be useful for developing SAR studies following the identification of initial `hits' during screening. In the case of aromatic functionalizing agents, the ring substitution pattern and the electronic nature of the substituents were varied to afford both electron rich and electron poor aromatic analogs. Aliphatic functionalizing agents were chosen to generate norbenzomorphan derivatives having substituents with varying degrees of non-polar surface area. For reductive aminations, the excess aldehyde helped compensate for the loss of a portion of reagent via reduction to the alcohol. The reaction of amines **22** and **23** with acylating agents, isothiocyanates and acrylates were conducted in the presence of triethylamine at room temperature to provide norbenzomorphan derivatives **27–36**. It was found that the addition of triethylamine to the reactions of **22** and **23** with acrylates and isothiocyanates gave improved product yields, and it is suggested that the triethylamine helps to facilitate the reaction by acting as a proton transfer agent.

The piperazine-coupled norbenzomorphans **20**{*1–2*,*1*} represent a new class of compounds, and arylpiperazines are themselves considered to be privileged structures.[1f] Accordingly, we prepared a small set of derivatives possessing this motif by functionalizing the free nitrogen atom in **20**{*1–2*,*1*} to afford products that varied in terms of Lewis bacisity as well as the number of hydrogen bond donors and acceptors (Scheme 5, Table 5, Figure 3). An amine (**37**), amides (**38**), sulfonamides (**39**) and thioureas (**40**) were obtained in moderate to good yield.

BIOLOGICAL ACTIVITY

Biological screening of the 124 member norbenzomorphan library is currently underway in the NIH's Molecular Library Probe Production Center Network (MLPCN), the National Institute of Mental Health's (NIMH) Psychoactive Drug Screening Program (PDSP), and Eli Lilly's Open Innovation Drug Discovery (OIDD) Program in order to identify biological probes and potential leads for new therapeutics. The assays are comprised of both phenotypic and target-based modules, which are useful for interrogating complex cellular systems as well as assessing enzymatic activity and receptor-ligand binding, respectively. These collaborations have unveiled some interesting biological activities which have not been previously associated with the norbenzomorphan class of compounds. Some of these data obtained from the MLPCN are detailed herein (Table 6).

It is noteworthy that inhibitors of both striatal-enriched protein tyrosine phosphatase (STEP)[16] and fatty acid synthase (FAS)[17] are being investigated as potential therapeutics for the treatment of Alzheimer's Disease (AD) and cancer, respectively (Table 6). STEP is a brain specific tyrosine phosphatase that is elevated in AD patients. Recent work suggests that decreasing STEP levels in the prefrontal cortex can mitigate the cognitive deficits from AD. Furthermore, FAS is overexpressed in many cancers and is believed to be essential for the growth of solid tumors. It has been demonstrated that inhibition of FAS can induce apoptosis in cancer cells. Accordingly, compounds that exhibit selective inhibition of these targets could lead to advances in the development of drugs relevant to these diseases.

SUMMARY

We have prepared a 124 membered library of novel norbenzomorphans by employing a sequential MCAP/RCM/Heck reaction sequence to generate the unsaturated azabicycle core, which was subsequently reduced to the target scaffold under ionic conditions. Utilizing a series of palladium catalyzed cross-coupling reactions and nitrogen functionalizations, the synthesis of a diverse set of norbenzomorphans bearing functional groups with varying electronic properties and substitution patterns was achieved. A complete Lipinski analysis of a representative group of 40 compounds expressing maximal diversity of substituents and aromatic substitution patterns was performed (see supporting information). Only one compound was found to violate more than one Lipinski parameter, suggesting that the majority of library members are expected to have desirable physiochemical properties.[23] Preliminary biological screening has identified `hits' that could serve as starting points for `lead' development. The wide range of biological activities associated with members of this library lends support to the `privileged scaffold' approach towards the identification of novel drug leads across a range of biological targets. SAR studies involving select `hit' compounds are ongoing to facilitate the development of `leads' for small molecule probes and therapeutics. Further applications of this and related approaches to the synthesis of medicinally relevant compound libraries are in progress, and the results of these investigations will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Institutes of Health (GM 86192 and GM 24539) and the Robert A. Welch Foundation (F-0652) for their generous support of this work. We are also grateful to Dr. Richard Pederson (Materia, Inc.) for catalyst support.

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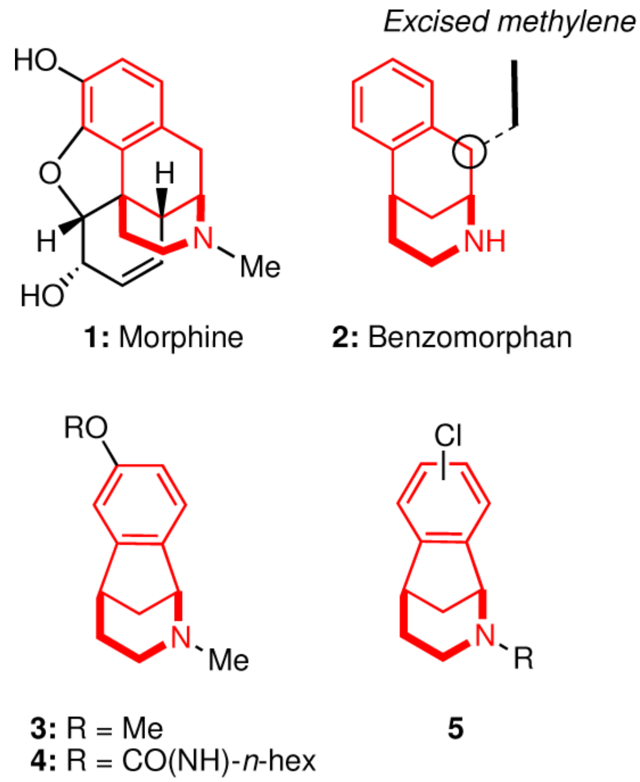

Figure 1.
Morphine (1), benzomorphan (2) and norbenzomorphans 3–5.

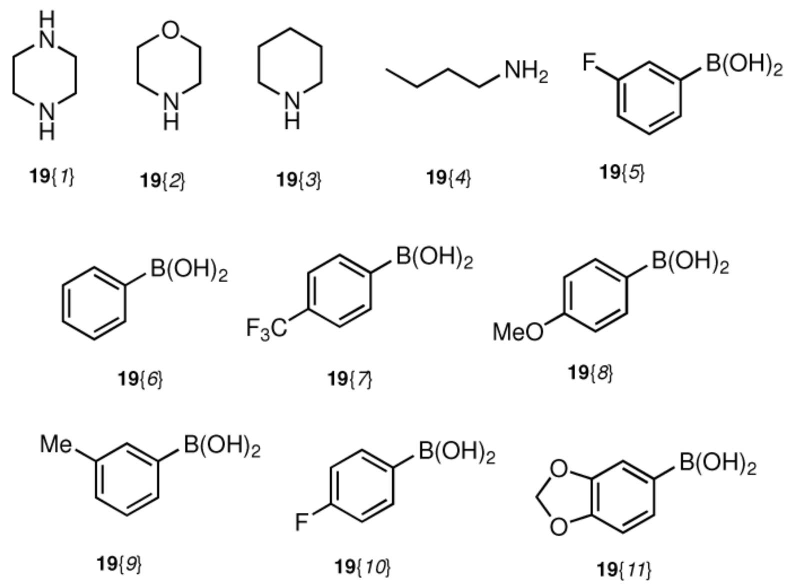

Figure 2.

Reagents used for cross-coupling reactions with 18{*1–3*}.

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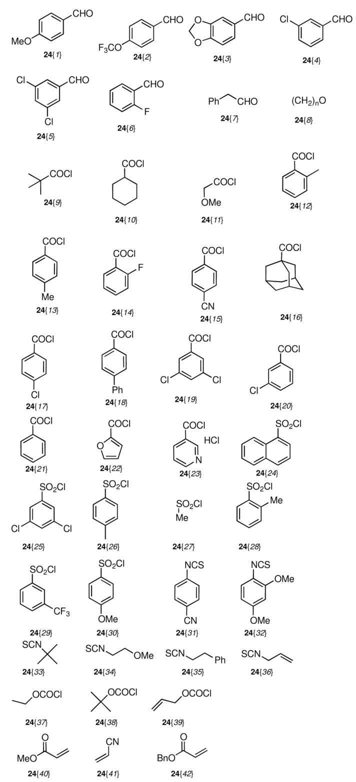
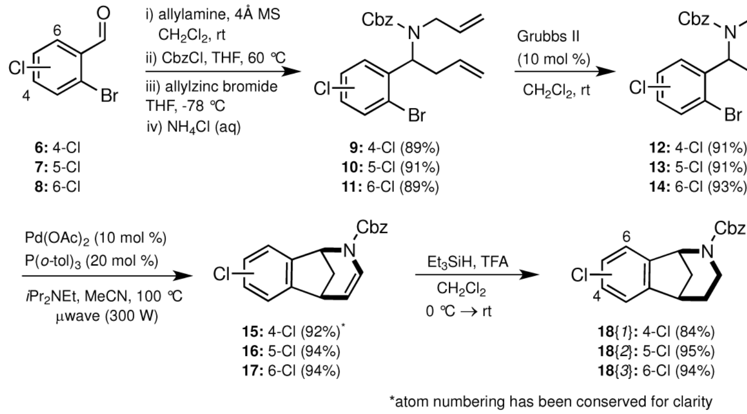
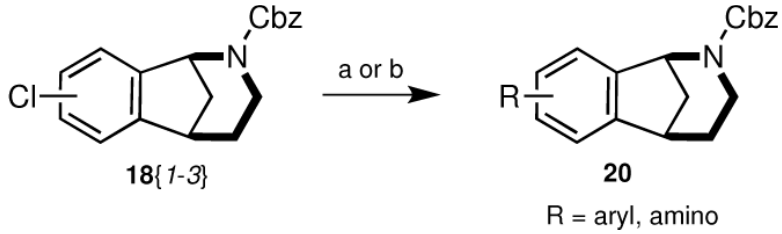


Figure 3.
N-Functionalizing agents.



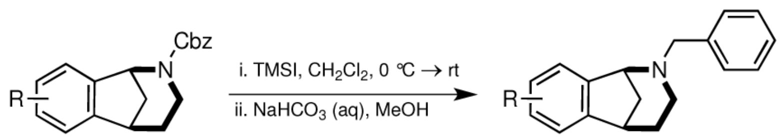
Scheme 1. Synthesis of norbenzomorphans 18{*1*–*3*}

*atom numbering has been conserved for clarity

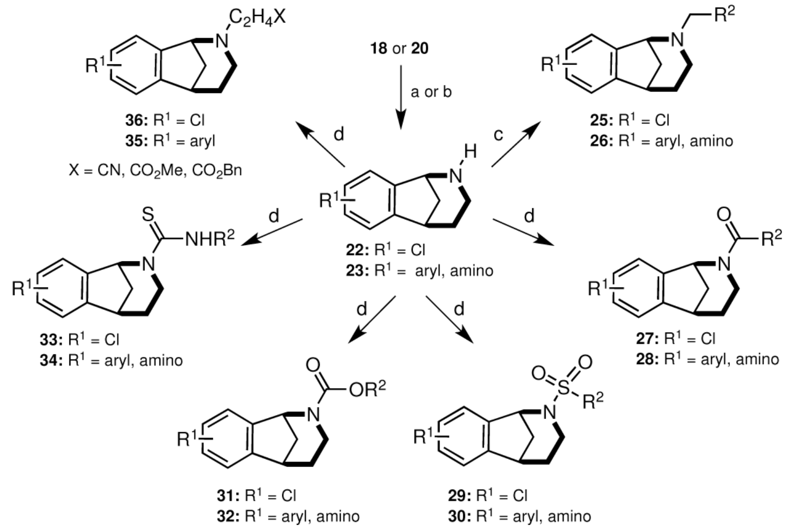


Scheme 2. Palladium catalyzed cross-coupling with norbenzomorphan chemset 18

Conditions: a) **19**{*1–4*}, $Pd(OAc)_2$ (5 mol %), JohnPhos®, NaO^tBu, toluene, 100 °C. b) **19**{*5–11*}, $Pd(P^tBu_3)_2$ (5 mol %), Cs_2CO_3, 1,4-dioxane, 100 °C.

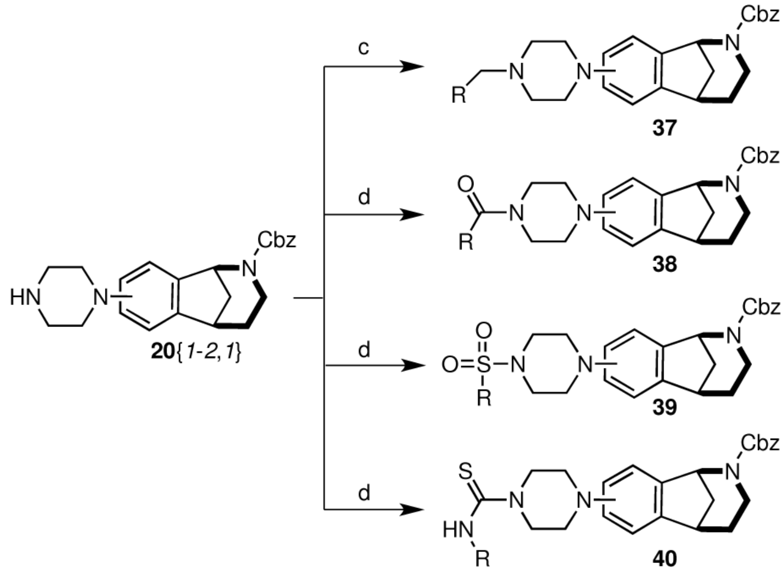


Scheme 3.
TMSI promoted benzylation.



Scheme 4. Derivatization of 22 and 23

Conditions: a) i. TMSI, CH_2Cl_2, 0 °C → rt, ii. MeOH/HCl. b) 10% Pd/C, EtOH, H_2 (1 atm). c) **24**{*1–8*}, 1,2-dichloroethane, $NaBH(OAc)_3$, AcOH. d) **24**{*9–42*}, NEt_3, CH_2Cl_2.



Scheme 5. Derivatization of piperazines 20{*1–2,1*}

Conditions: See scheme 4.

Table 1

Cross-coupling reactions with 18{*1*–*3*}.

Entry	Scaffold	Coupling Agent	Product	Yield (%)
1	**18**{*1*}	**19**{*1*}	**20**{*1,1*}	75
2	**18**{*1*}	**19**{*2*}	**20**{*1,2*}	88
3	**18**{*1*}	**19**{*5*}	**20**{*1,5*}	60
4	**18**{*2*}	**19**{*1*}	**20**{*2,1*}	72
5	**18**{*2*}	**19**{*2*}	**20**{*2,2*}	97
6	**18**{*2*}	**19**{*3*}	**20**{*2,3*}	67
7	**18**{*2*}	**19**{*4*}	**20**{*2,4*}	66
8	**18**{*2*}	**19**{*6*}	**20**{*2,6*}	98
9	**18**{*2*}	**19**{*7*}	**20**{*2,7*}	86
10	**18**{*2*}	**19**{*8*}	**20**{*2,8*}	94
11	**18**{*2*}	**19**{*9*}	**20**{*2,9*}	89
12	**18**{*2*}	**19**{*10*}	**20**{*2,10*}	94
13	**18**{*2*}	**19**{*11*}	**20**{*2,11*}	73
14	**18**{*3*}	**19**{*2*}	**20**{*3,2*}	69
15	**18**{*3*}	**19**{*7*}	**20**{*3,7*}	88
16	**18**{*3*}	**19**{*8*}	**20**{*3,8*}	86
17	**18**{*3*}	**19**{*6*}	**20**{*3,6*}	82

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Table 2

Benzylamines 21 from carbamates 18 and 20.

Entry	Carbamate	Benzylamine	Yield (%)
1	**18**{*2*}	**21**{*2*}	88
2	**20**{*1,2*}	**21**{*1,2*}	55
3	**20**{*2,11*}	**21**{*2,11*}	79
4	**20**{*2,7*}	**21**{*2,7*}	91
5	**20**{*2,8*}	**21**{*2,8*}	78
6	**20**{*2,4*}	**21**{*2,4*}	79
7	**20**{*2,3*}	**21**{*2,3*}	96
8	**20**{*2,6*}	**21**{*2,6*}	95
9	**20**{*3,2*}	**21**{*3,2*}	66
10	**20**{*3,7*}	**21**{*3,7*}	72

Table 3

Deprotection of 18 and 20.

Entry	Carbamate	Free amine	Yield(%)
1	**18**{*2*}	**22**{*2*}	98[a]
2	**18**{*3*}	**22**{*3*}	95[a]
3	**20**{*2,2*}	**23**{*2,2*}	87[a]
4	**20**{*2,3*}	**23**{*2,3*}	88[a]
5	**20**{*2,6*}	**23**{*2,6*}	80[a]
6	**20**{*2,7*}	**23**{*2,7*}	98[b]
7	**20**{*2,8*}	**23**{*2,8*}	94[b]
8	**20**{*2,9*}	**23**{*2,9*}	77[b,c]
9	**20**{*2,10*}	**23**{*2,10*}	87[a]
10	**20**{*2,11*}	**23**{*2,11*}	93[a]
11	**20**{*3,7*}	**23**{*3,7*}	76[a]

[a] TMSI

[b] $Pd(0)/H_2$

[c] crude yield

Table 4

N-Functionalization of 22 and 23.

Entry	Free amine	Function alizing agent	Product	Yield(%)
1	**22**{*2*}	**24**{*1*}	**25**{*2,1*}	72
2	**22**{*2*}	**24**{*9*}	**27**{*2,9*}	88
3	**22**{*2*}	**24**{*9*}	**27**{*2,9*}	40
4	**22**{*2*}	**24**{*11*}	**27**{*2,11*}	71
5	**22**{*2*}	**24**{*12*}	**27**{*2,12*}	95
6	**22**{*2*}	**24**{*24*}	**29**{*2,24*}	87
7	**22**{*2*}	**24**{*25*}	**29**{*2,25*}	77
8	**22**{*2*}	**24**{*26*}	**29**{*2,26*}	68
9	**22**{*2*}	**24**{*37*}	**31**{*2,37*}	74
10	**22**{*2*}	**24**{*38*}	**31**{*2,38*}	88
11	**22**{*2*}	**24**{*40*}	**36**{*2,40*}	81
12	**23**{*2,11*}	**24**{*9*}	**28**{*2,11,9*}	80
13	**23**{*2,11*}	**24**{*10*}	**28**{*2,11,10*}	98
14	**23**{*2,11*}	**24**{*13*}	**28**{*2,11,13*}	55
15	**23**{*2,11*}	**24**{*14*}	**28**{*2,11,14*}	98
16	**23**{*2,11*}	**24**{*18*}	**28**{*2,11,18*}	74
17	**23**{*2,11*}	**24**{*19*}	**28**{*2,11,19*}	56
18	**23**{*2,11*}	**24**{*24*}	**30**{*2,11,24*}	59
19	**23**{*2,11*}	**24**{*29*}	**30**{*2,11,29*}	57
20	**23**{*2,11*}	**24**{*30*}	**34**{*2,11,30*}	53
21	**23**{*2,11*}	**24**{*31*}	**34**{*2,11,31*}	72
22	**23**{*2,11*}	**24**{*32*}	**34**{*2,11,32*}	53
23	**23**{*2,11*}	**24**{*33*}	**34**{*2,11,33*}	80
24	**23**{*2,11*}	**24**{*34*}	**34**{*2,11,34*}	70
25	**23**{*2,11*}	**24**{*35*}	**34**{*2,11,35*}	98
26	**23**{*2,6*}	**24**{*15*}	**28**{*2,6,15*}	91
27	**23**{*2,6*}	**24**{*17*}	**28**{*2,6,17*}	85
28	**23**{*2,6*}	**24**{*27*}	**30**{*2,6,27*}	61
29	**23**{*2,7*}	**24**{*7*}	**26**{*2,7,7*}	75
30	**23**{*2,7*}	**24**{*8*}	**26**{*2,7,8*}	87
31	**23**{*2,8*}	**24**{*2*}	**26**{*2,8,2*}	77
32	**23**{*2,8*}	**24**{*9*}	**28**{*2,8,9*}	53
33	**23**{*2,8*}	**24**{*10*}	**28**{*2,8,10*}	86
34	**23**{*2,8*}	**24**{*16*}	**28**{*2,8,16*}	51
35	**23**{*2,8*}	**24**{*28*}	**30**{*2,8,28*}	62
36	**23**{*2,8*}	**24**{*39*}	**32**{*2,8,39*}	55
37	**23**{*2,8*}	**24**{*41*}	**35**{*2,8,41*}	84
38	**23**{*2,9*}	**24**{*1*}	**26**{*2,9,1*}	59
39	**23**{*2,9*}	**24**{*3*}	**26**{*2,9,3*}	73

Entry	Free amine	Function alizing agent	Product	Yield(%)
40	**23**{*2,9*}	**24**{*8*}	**26**{*2,9,8*}	66
41	**23**{*2,9*}	**24**{*39*}	**32**{*2,9,39*}	95
42	**23**{*2,9*}	**24**{*40*}	**35**{*2,9,40*}	83
43	**23**{*2,10*}	**24**{*3*}	**26**{*2,10,3*}	71
44	**23**{*2,10*}	**24**{*12*}	**28**{*2,10,12*}	81
45	**23**{*2,10*}	**24**{*15*}	**28**{*2,10,15*}	82
46	**23**{*2,10*}	**24**{*20*}	**28**{*2,10,20*}	67
47	**23**{*2,10*}	**24**{*25*}	**30**{*2,10,25*}	71
48	**23**{*2,3*}	**24**{*4*}	**26**{*2,3,4*}	75
49	**23**{*2,3*}	**24**{*10*}	**28**{*2,3,10*}	61
50	**23**{*2,3*}	**24**{*14*}	**28**{*2,3,14*}	63
51	**23**{*2,3*}	**24**{*15*}	**28**{*2,3,15*}	53
52	**23**{*2,3*}	**24**{*19*}	**28**{*2,3,19*}	56
53	**23**{*2,2*}	**24**{*5*}	**26**{*2,2,5*}	96
54	**23**{*2,2*}	**24**{*6*}	**26**{*2,2,6*}	70
55	**23**{*2,2*}	**24**{*8*}	**26**{*2,2,8*}	92
56	**23**{*2,2*}	**24**{*20*}	**28**{*2,2,20*}	75
57	**23**{*2,2*}	**24**{*30*}	**30**{*2,2,30*}	62
58	**22**{*1*}	**24**{*22*}	**28**{*1,22*}	60
59	**22**{*1*}	**24**{*23*}	**28**{*1,23*}	66
60	**22**{*1*}	**24**{*31*}	**33**{*1,31*}	60
61	**22**{*1*}	**24**{*32*}	**33**{*1,32*}	60
62	**22**{*1*}	**24**{*33*}	**33**{*1,33*}	66
63	**22**{*1*}	**24**{*34*}	**33**{*1,34*}	71
64	**22**{*1*}	**24**{*35*}	**33**{*1,35*}	66
65	**22**{*1*}	**24**{*36*}	**33**{*1,36*}	68
66	**22**{*1*}	**24**{*42*}	**36**{*1,42*}	67
67	**23**{*3,7*}	**24**{*3*}	**26**{*3,7,3*}	55
68	**23**{*3,7*}	**24**{*8*}	**26**{*3,7,8*}	93
69	**23**{*3,7*}	**24**{*11*}	**28**{*3,7,11*}	81
70	**23**{*3,7*}	**24**{*30*}	**30**{*3,7,30*}	85
71	**23**{*3,7*}	**24**{*35*}	**34**{*3,7,35*}	89
72	**23**{*3,7*}	**24**{*39*}	**32**{*3,7,39*}	73

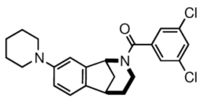
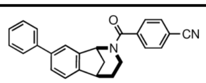
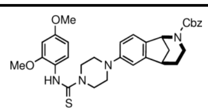
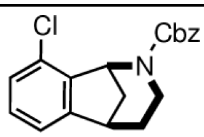
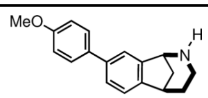
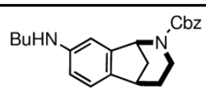
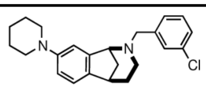
Table 5

Library derived from 20{*1–2,1*}.

Entry	Piperazine	*N*-functionali zing Reagent	Product	Yield (%)
1	**20**{*1,1*}	**24**{*3*}	**37**{*1,1,3*}	58
2	**20**{*1,1*}	**24**{*21*}	**38**{*1,1,21*}	54
3	**20**{*1,1*}	**24**{*32*}	**40**{*1,1,32*}	68
4	**20**{*1,1*}	**24**{*9*}	**38**{*2,1,9*}	96
5	**20**{*2,1*}	**24**{*13*}	**38**{*2,1,13*}	93
6	**20**{*2,1*}	**24**{*18*}	**38**{*2,1,18*}	92
7	**20**{*2,1*}	**24**{*20*}	**39**{*2,1,20*}	97
8	**20**{*2,1*}	**24**{*35*}	**40**{*2,1,35*}	60
9	**20**{*2,1*}	**24**{*25*}	**39**{*2,1,25*}	68
10	**20**{*2,1*}	**24**{*29*}	**39**{*2,1,29*}	53
11	**20**{*2,1*}	**24**{*30*}	**39**{*2,1,30*}	54

Table 6

Biological activity of select norbenzomorphans.

Entry	Compound	Activity*	Potency
1	 **28**{*2,3,19*}	human M_1 muscarinic receptor antagonist[18]	69% (3uM)
2	 **28**{*2,6,15*}	striatal-enriched protein tyrosine phosphatase (STEP) inhibitor[16]	69% (20 uM)
3	 **40**{*1,1,32*}	fatty acid synthase inhibitor[17]	57% (15uM)
4	 **18**{*3*}	Y. pestis topoisomerase I inhibitor[19]	61% (10 uM)
5	 **23**{*2,8*}	mycobacterium tuberculosis bioA enzyme inhibitor[20]	91% (10 uM)
6	 **20**{*2,4*}	microphthalmia-associated transcription factor (MITF) activator[21]	3.3 uM (AC_{40})
7	 **26**{*2,3,4*}	serotonin 5A receptor (5HTR5A) inverse agonist[22]	27% (9.3 uM)

*an `active' compound is defined individually by each assay provider; see references 16–22.