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The pipecolic linker—an acid-labile handle for derivatization of secondary amines on a solid-support. Part 3

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This manuscript is dedicated to the initiators of bilateral cooperation: Dr. Zygmunt Ryznerski, Professor Alfred Zejc, Dr. Pierre Chevallet, and Professor Jean Castel

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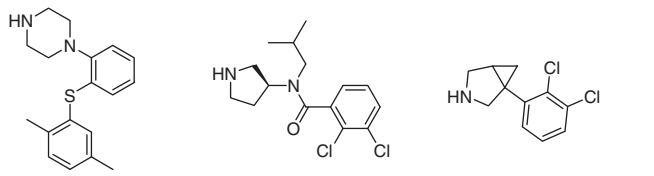
ABSTRACT

Herein, we demonstrate the versatility of the pipecolic linker for the structural diversification of secondary amines with potential CNS activity. The solid-phase methods elaborated involved N1-indole sulfonylation, nitroindole and nitroarene reduction, and microwave-assisted Buchwald–Hartwig N-arylation.

Since the monumental work of Merrifield who introduced a new paradigm within organic chemistry, termed solid-phase synthesis, this technique has become the method of choice for the preparation of peptides and peptidomimetics. An increasing demand for the synthesis of structurally diverse compound libraries has contributed to the translation of a large number of reactions from solution to the solid-phase. In the mid 1990s, the application of solid-supported methods was extended to the synthesis of small organic compounds.[1–3] As a consequence, several examples have shown that high-throughput chemistry, based on solid-supported methods, is efficient in the pharmaceutical industry and in academic research for exploring chemical space and acquiring meaningful structure–activity relationship data for drug discovery projects.[4–6] Recent developments in the area of DNA-encoded libraries bring new opportunities for the application of high-throughput chemistry methods for the synthesis of small molecule and peptide-derived libraries, and may have a significant impact on drug development processes.[7]

Part of our work has focused on the development of solid-supported methods for the discovery and establishing structure–activity relationships among biologically active compounds targeted on CNS receptors. Recent progress in the area has been made via evaluation of compounds derived from secondary alicyclic amines. Such compounds may be regarded as attractive drug templates for the design of agonists/antagonists of monoamine receptors as well as inhibitors of serotonin (5-HT), noradrenalin (NA), and dopamine (D) transporters (Fig. 1).[8–10]



vortioxetine
multimodal 5-HT agent

PF-184298
5-HT/NA reuptake inhibitor

DOV 21,947
5-HT/NA/D reuptake inhibitor

Figure 1. Selected CNS active secondary amine derivatives (5-HT—serotonin; NA—noradrenaline; D—dopamine).

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It is worth noting, that the aforementioned compounds have been, among others, identified from the screening libraries generated on solid-supports. The method of choice for the solid-phase synthesis of such derivatives involves commercially available acid-labile linkers, for example, 4-carboxychlorotrityl linkers or carbamate/carbonate linkers. However, these handles suffer from low anchoring yields and high sensitivity to acidic conditions. As an alternative, we proposed the pipecolic linker (Pip-linker) as a versatile acid-labile anchor for the derivatization of diverse primary and secondary amines.[11]

Compared to other linkers, for example, BAL, Wang, the Pip-linker has the unique property of regenerating its carboxylic function after release of the products under acidic conditions, which enables recycling of the Pip-resin several times. The mechanism of regeneration involves an oxazolinium-5-one as an intermediate, and it is favored by the spatial conformation and electron-donating effect of an acyl substituent (cyclohexanecarbonyl) which acts as a spacer between the resin and the pipecolic acid.[12]

The pipecolic linker was recently evaluated as an anchor for structural modifications of aliphatic and aromatic amines, alcohols, phenols, and hydrazides. The Pip-linker could also be used for SPPS in the reverse N-to-C direction, for the synthesis of pseudopeptides and cyclic peptides, as well as in the production of vinylogous γ-amino acids, urea-derived peptides, and peptide alcohols (Fig. 2).[13]

Herein, we present the application of the pipecolic linker for the synthesis of small organic compounds for the development of CNS active agents. As the synthetic template we chose indole and phenylpiperazine scaffolds for structural diversification of 1-arylsulfonyl-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indoles (set I), 5-arylsulfonylamino-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indoles (set II), and 1-(3-arylsulfonylphenyl)piperazine derivatives (set III) (Fig. 3). Although many solution-phase methods have been explored for the synthesis of such derivatives, to the best of our knowledge, no universal solid-phase synthetic approaches for sets I and II have been reported.[14,15]

To evaluate the Pip linker functionalized polystyrene resin in the synthesis of small organic compounds, we first investigated a solid-phase method for the generation of a series of 1-arylsulfonyl-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole derivatives (Scheme 1). The first building block was attached to the support under classic BOP activation to yield resin-bound 4-piperidone 2. This was further submitted to condensation with an indole derivative resulting in 1,2,3,6-tetrahydropyridin-4-yl-1*H*-indole derivative 3. A critical step in the preparation of 1-arylsulfonyl-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indoles is sulfonylation of the resin-bound indole moiety at nitrogen. Various conditions were tested using different deprotonating agents in organic or biphasic mediums. First attempts were carried out with unsubsituted indole and various bases (potassium, sodium *tert*-butoxide, sodium hydroxide, or sodium hydride). Among the tested conditions, NaH gave the best result (entry 5). However, with this traditional deprotonating agent, sulfonylation depended highly upon the indole moiety substitution pattern (Table 1, entries 5–8).

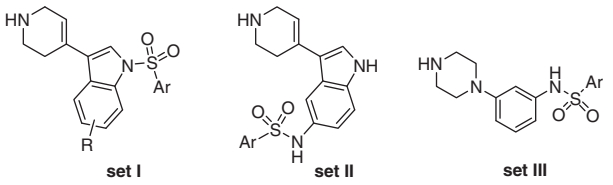
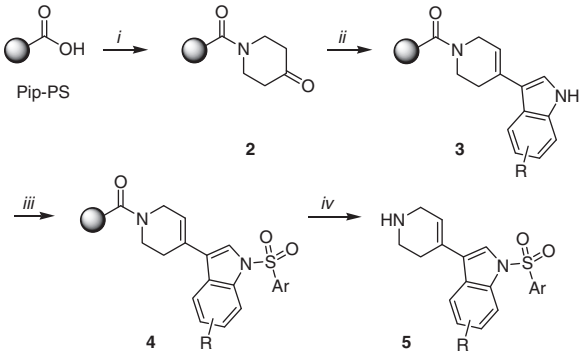


Figure 3. Selected secondary amine derivatives with potential CNS activity.



Scheme 1. Solid-phase synthesis of 1-arylsulfonyl-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indoles (set I). Reagents and conditions: (i) 4-piperidone hydrochloride monohydrate, BOP, DIEA, DMF, 2 h, rt; (ii) indole, KOH, THF/MeOH (3/7, v/v), 20 h, 60 °C; (iii) arylsulfonyl chloride, BTPP, NMP, 24 h, rt; (iv) TFA/CH_2Cl_2 (8/2, v/v), 2 h, rt.

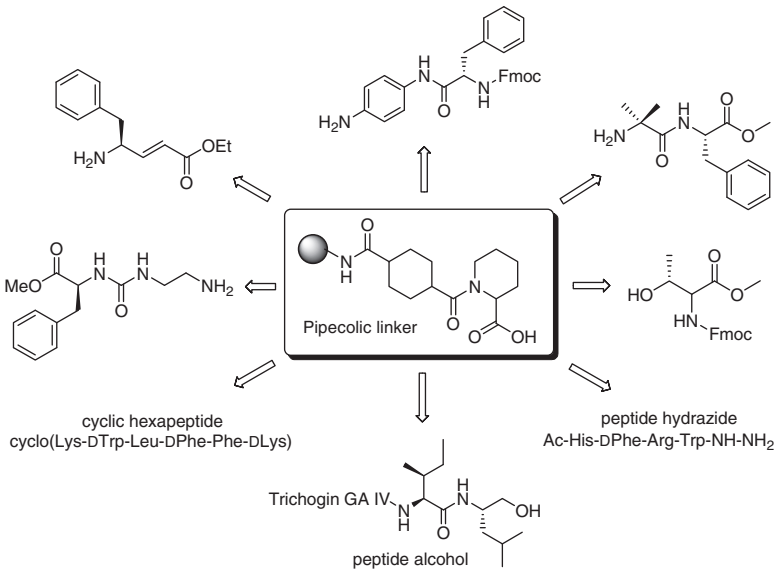


Figure 2. The diverse applications of the pipecolic linker.

Table 1
Sulfonylation of indoles **3** at nitrogen on a solid support

Entry	Resin-bound indole deri-vative (R=)	4-F-benzenesulfonyl Cl (equiv)	Base (equiv)	Solvent	Temp	Time (h)	Conversion[a] (%)
1	H	10	KO*t*Bu[20]	THF	rt	14	0
2	H	6	NaOH/TBAB[40/0.5]	toluene/MeOH(3/7)	60 °C	19	0
3	H	30	NaOH/TBAHS[60/2]	toluene/H_2O(1/1)	rt	24	0
4	H	40	NaO*t*Bu[80]	DMF	rt	24	0
5	H	20	NaH[40]	THF	rt	24	98
6	5-MeO	30	NaH[50]	THF	rt	24	21
7	5-MeO	40	NaH[50]	THF	rt	24	45
8	6-Cl	50	NaH[60]	THF	rt	24	72
9	H	20	BTPP[40]	NMP	rt	24	99
10	5-MeO	20	BTPP[40]	NMP	rt	24	97
11	6-Cl	20	BTPP[40]	NMP	rt	24	99

[a] Conversion was calculated based on the peak area integration during LC/MS analysis of cleaved compounds at a sum of wavelengths between 200 and 270 nm.

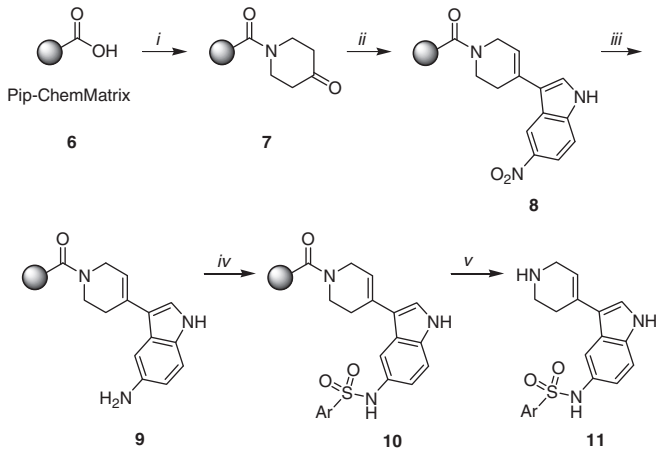
Table 2
Cleavage yields of compounds synthesized on Pip-PS resin

Product	R	Ar	Yield[a] (%)	Purity[b] (%)
5a	6-Cl	4-F-C_6H_4	48	99
5b	6-Cl	3-Me-C_6H_4	42	100
5c	5-MeO	4-F-C_6H_4	43	98

[a] Yields are based on the weight of purified products relative to the initial loading of the resin (1.3 mmol/g).
[b] Percent purity of the product was calculated based on the peak area integration during LC/MS analysis of cleaved compounds at a sum of wavelengths between 200 and 270 nm.

To minimize variability we proposed an alternative indole-1 sulfonylation procedure, which involved strong, non-ionic, basic conditions employing BTPP [*tert*-butylimino-tri(pyrrolidino)phosphorane] in CH_2Cl_2, a valuable tool, for example, in peptide,[16,17] heterocyclic,[18] and macrocyclic chemistry.[19] In our case, the sulfonylation was efficient for the three tested indole derivatives (Table 1, entries 9–11). To illustrate the versatility of this chemistry, compounds **5a–c** were prepared (Table 2). The final products were released from the resin by TFA/CH_2Cl_2 treatment. After purifying by preparative LC/MS, pure products **5a–c** were obtained in moderate yields and excellent purities.

In the next step, we envisaged the synthesis of 5-arylsulfonyl-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indoles (set II). Starting from Pip-PS resin we adopted similar conditions for attachment of 5-nitroindole to the resin (Scheme 2). Nitro derivative 8 was subsequently submitted to reduction.



Scheme 2. Solid-phase synthesis of 5-arylsulfonylamino-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indoles (set II). Reagents and conditions: (i) 4-piperidone hydrochloride monohydrate, BOP, DIEA, DMF, 2 h, rt; (ii) 5-nitroindole, KOH, THF/MeOH (3/7, v/v), 20 h, 60 °C; (iii) $Na_2S_2O_4$, K_2CO_3, NMP/H_2O (3/7, v/v), 12 h, rt; (iv) $ArSO_2Cl$, Py/CH_2Cl_2 (1/4, v/v), 2 × 12 h, rt; (v) TFA/CH_2Cl_2 8/2, 2 h, rt.

All the approaches investigated, either in organic or in biphasic systems additionally involving catalysts, failed to afford the amino derivative when using reducing agents under basic conditions and Pip-PS resin (Table 1-SI).[20,21] This might be explained by the low swelling properties of the polystyrene resin in aqueous medium. We thus decided to anchor the pipecolic linker on hydrophilic amino ChemMatrix resin (loading 1.14 mmol/g), and the synthesis was performed again (Scheme 2). In contrast to that observed with Pip-PS, sodium dithionite allowed us to reduce 5-nitroindole bound to the pipecolic linker in a mixture of NMP/H_2O (Table 3). Subsequent sulfonylation of 5-aminoindole derivative 9 with arylsulfonyl chloride in a mixture of pyridine and CH_2Cl_2 at room temperature gave access to the desired 5-arylsulfonylamino-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indoles. These conditions were applied for the synthesis of compounds **11a–c** (Table 4).

Finally, we used the Pip linker for the synthesis of 1-(3-arylsulfonylphenyl)piperazine derivatives 15 (set III, Scheme 3). Piperazine was easily anchored to the resin via BOP-promoted coupling. The product was subsequently submitted to palladium-catalyzed amination optimization with 1-bromo-3-nitrobenzene using Buchwald–Hartwig conditions. The yields and purities reported for this reaction on the solid-phase depended highly on the type of support, the linker, the halogen atom, and the substitution pattern of the aryl halide.[22–24]

Under traditional prolonged heating of 1-bromo-3-nitrobenzene in toluene low conversion to the desired product **13** was detected (Table 5, entries 1–3). Therefore, we decided to run this reaction under microwave irradiation. A mixture of 1,4-dioxane/*t*-butanol was found to be well suited for MW conditions. A reaction time of 15 min allowed for conversion of all free amino groups (Table 5). Prolonged MW heating or repetitions did not increase the conversion.

The subsequent reduction of resin-bound nitropiperazine derivative **13** under basic conditions using sodium dithionite/potassium carbonate in water/THF (1/1; v/v), for 5 d yielded the expected 3-amino derivative **14**.

The latter was submitted to sulfonylation, using four different sulfonyl chlorides, in a mixture of pyridine and CH_2Cl_2 (1/4; v/v). The final compounds **15a–15d** were purified using preparative LC/MS (Table 6).

In summary, we have demonstrated new applications of a pipecolic linker for the synthesis of small organic compounds. Three efficient solid-phase synthetic approaches for the synthesis of 1-arylsulfonyl-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indoles (set I), 5-arylsulfonylamino-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indoles (set II), and 3-arylsulfonyl-phenylpiperazine derivatives (set III) were developed. Regardless of the indole substitution pattern, sulfonylation at position 1 of the indole-bound PS-Pip resin was accomplished using BTPP (a strong base) in CH_2Cl_2. Reduction of 5-nitroindoles (set II), in aqueous medium under basic conditions

Table 3
Reduction of the nitro function on the Pip-ChemMatrix resin

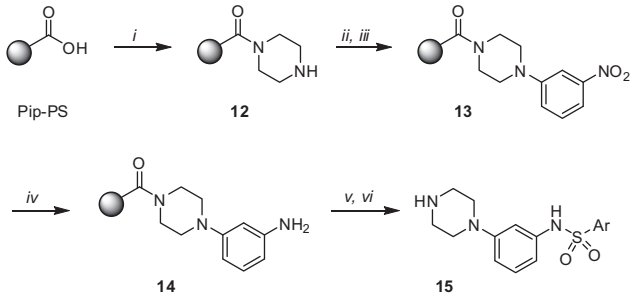
Entry	Reducing agent (equiv)	K_2CO_3 (equiv)	Solvent	Temp	Time (h)	Conversion[a] (%)
1	$SnCl_2$ [150]	—	NMP/EtOH	rt	16	0
2	$SnCl_2$ [150]	—	DMF/H_2O (9/1)	40 °C	20	0
3	$Na_2S \times 9H_2O$ [20]	20	DMF/H_2O (9/1)	60 °C	72	60
4	$Na_2S \times 9H_2O$ ethyl viologen [20/0.02]	20	DMF/H_2O (9/1)	rt	48	65
5	$Na_2S_2O_4$ [8]	8	H_2O	rt	12	97
6	$Na_2S_2O_4$ [10]	10	NMP/H_2O (3/7)	rt	12	98
7	$Na_2S_2O_4$ [15]	15	NMP/H_2O (3/7)	rt	12	100

[a] Calculated based on the peak area integration during LC/MS analysis of cleaved compounds at a sum of wavelengths between 200 and 270 nm.

Table 4
Sulfonylation of the primary amine on the Pip-ChemMatrix resin

Product	Ar	Yield[a] (%)	Purity[b] (%)
11a	4-F-C_6H_4	40	100
11b	4-Me-C_6H_4	37	97
11c	2-Naphthyl	37	99

[a] Yields are based on the weight of purified products relative to the initial loading of the resin (1.14 mmol/g).
[b] Percent purity of the product was calculated based on integration of the peak area during LC/MS analysis of cleaved compounds at a sum of wavelengths between 200 and 270 nm.



Scheme 3. Solid-phase synthesis of 1-(3-arylsulfonyl-phenyl)piperazine derivatives (set III). Reagents and conditions: (i) piperazine, BOP, DIEA, DMF, 2 h, rt; (ii) 1-bromo-3-nitrobromobenzene, Pd_2dba_3, BINAP, NaO*t*Bu, *t*BuOH/1,4-dioxane (1/2, v/v), 15 min, 130 °C MW; (iii) Ac_2O, DIEA, CH_2Cl_2, 2 × 20 min, rt; (iv) $Na_2S_2O_4$, K_2CO_3, THF/H_2O (3/7, v/v), 5 d, rt; (v) $ArSO_2Cl$, Py/CH_2Cl_2 (1/4, v/v), 2 × 12 h, rt; (vi) TFA/CH_2Cl_2 (8/2, v/v), 2 h, rt.

using $Na_2S_2O_4$ and ChemMatrix-Pip resin, enabled structural diversification of the 5-arylsulfonyl indole derivatives on the solid-support. Last but not least, N-arylation under MW irradiation, followed by reduction of the nitro group in an aqueous medium and sulfonylation allowed structural diversification of the arylpiperazine derivatives on the pipecolic linker. These procedures allow for the application of high-throughput synthesis methods for designing compound libraries for screening campaigns aimed at selection of the most promising secondary amine derivatives with potential applications in psychiatric disorders of the central nervous system such as depression, schizophrenia, or neurodegenerative disorders.

Table 6
Cleavage yields of compounds **15** synthesized on Pip-PS resin

Product	Ar	Yield[a] (%)	Purity[b] (%)
15a	C_6H_5	37	99
15b	4-F-C_6H_4	43	99
15c	3-Me-C_6H_4	40	100
15d	2-Thienyl	36	98

[a] Yields are based on the weight of purified products and are relative to the initial loading of the resin (1.14 mmol/g).
[b] Percent purity of the purified product was calculated based on the peak area integration during LC/MS analysis of cleaved compounds at a sum of wavelengths between 200 and 270 nm.

Condensation of indole derivatives to resin-bound piperidone on Pip-PS and Pip-ChemMatrix resins

To a solution of KOH (0.1 M) in MeOH/THF (3/7, v/v), 5-nitro-1*H*-indole (477 mg, 2.94 mmol, 5.5 equiv) or 5-methoxy-1*H*-indole (433 mg, 0.81 mmol, 5.5 equiv) or 6-chloro-1*H*-indole (446 mg, 2.94 mmol, 5.5 equiv) was added. The mixture was added to the PS resin (500 mg, 0.4 mmol, 0.8 mmol g^{-1}) or ChemMatrix resin (500 mg, 0.535 mmol, 1.07 mmol g^{-1}) and heated to 60 °C for 20 h with occasional shaking. The resulting resin products were washed with H_2O (3×), THF (3×), DMF, MeOH (1×), and CH_2Cl_2 (2×) and dried under vacuum.

Sulfonylation of resin-bound N1-indole derivatives on Pip-PS resin

To 100 mg of resin-bound 3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole derivative **4** a mixture of BTPP (1 mL, 3.28 mmol) in CH_2Cl_2 (4 mL) was added. After 4 min, arylsulfonyl chloride (1.64 mmol) in 0.5 mL of CH_2Cl_2 was added and the reaction was allowed to proceed at rt for 24 h. The resulting resin was washed thoroughly with DMF (4×), MeOH (1×), and CH_2Cl_2 (4×).

Reduction of the 5-nitroindole derivative on Pip-ChemMatrix resin

A mixture of sodium dithionite (1.37 g, 7.86 mmol, 15 equiv) and K_2CO_3 (1.1 g, 7.86 mmol, 15 equiv) in H_2O/NMP (7/3, v/v) (5 ml) was added to the resin (500 mg, 0.525 mmol, 1.05 mmol g^{-1}). The

Table 5
N-Arylation of piperazine derivatives

Entry	1-Br-3-NO_2 benzene (equiv)	Pd_2dba_3/BINAP (equiv)	NaO-*t*-Bu (equiv)	Solvent	Temp	Time (h)	Conversion[a] (%)
1	6	0.2/0.3	40	Toluene	80 °C	48	35
2	10	0.2/0.3	10	Toluene	80 °C	2 × 24	40
3	10	0.2/0.3	10	*t*BuOH/DME (1/1)	80 °C	2 × 24	45
4	10	0.2/0.3	10	*t*BuOH/1,4-dioxane (1/1)	130 °CMW	2 × 0.4	58
5	15	0.2/0.3	10	*t*BuOH/1,4-dioxane (1/1)	130 °CMW	2 × 0.4	60
6	10	0.2/0.3	10	*t*BuOH/1,4-dioxane (1/2)	130 °CMW	2 × 0.4	70
7	10	0.4/0.6	10	*t*BuOH/1,4-dioxane (1/2)	130°CMW	0.4	85

[a] Conversion calculated based on the peak area integration during LC/MS analysis of cleaved compounds at a sum of wavelengths between 200 and 270 nm.

resin was stirred gently for 12 h at rt, and then was washed with H_2O (2×), H_2O/DMF (1/1, v/v) (2×), DMF (2×), MeOH (1×), and CH_2Cl_2 (2×) and dried under vacuum.

Preparation 1-(3-nitrophenyl)piperazine on Pip-PS resin

Pip-PS resin (500 mg, 0.39 mmol, 0.78 mmol g^{-1}) was suspended in 5 mL of a mixture of anhydrous 1,4-dioxane/*tert*-butyl alcohol (2/1, v/v) in an oven-dried microwave reactor purged with argon. Next, 1-bromo-3-nitrobenzene (790 mg, 3.9 mmol, 10 equiv) was added to the resin. After stirring for 20 min at rt, Pd_2dba_3 (70 mg, 0.08 mmol, 0.4 equiv based on Pd), BINAP (145 mg, 0.125 mmol, 0.6 equiv), and NaO*t*Bu (375 mg, 3.9 mmol, 10 equiv) were added as solids. The reactor was purged with argon for a few minutes, and was placed into the microwave cavity of a 1600 W CEM Discovery multimode microwave. Initial microwave irradiation at 300 W was used, and the temperature was increased from rt to 130 °C, and held at this temperature for 15 min. After cooling the mixture to rt, it was transferred to a syringe, and washed with CH_2Cl_2 (1×), MeOH (1×), CH_2Cl_2 (1×), DMF (2×), THF (1×), MeOH (1×), and CH_2Cl_2 (3×) and dried under vacuum. The completion of the reaction was confirmed by a negative chloranil test. A mixture of Ac_2O (5 ml) and DIEA (6.33 ml) in CH_2Cl_2 (10 ml) was added to the resin and the mixture was stirred for 20 min. The acylation was repeated once more followed by washing with DMF (2×), MeOH (1×) and CH_2Cl_2 (2×) and drying under vacuum.

Reduction of 1-(3-nitrophenyl)piperazine on Pip-PS resin

Sodium dithionite (2.26 g, 13 mmol, 40 equiv) and K_2CO_3 (1.8 g, 13 mmol, 40 equiv) in a mixture of H_2O/THF (1/1, v/v) (30 ml) was added to the resin (500 mg, 0.325 mmol, 0.65 mmol g^{-1}). The mixture was stirred at rt for 5 d, then the resin was washed with H_2O (2×), H_2O/DMF (1/1, v/v) (2×), DMF (2×), MeOH, and CH_2Cl_2 (2×) and dried over P_2O_5 under vacuum for 24 h.

Characterization data for representative final compounds are summarized below. Experimental procedures and characterization data for the remaining compounds are in the Supplementary data.

6-Chloro-1-(4-fluoro-benzenesulfonyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole (5a)

Yield: 24 mg (48% isolated yield) as a yellow oil following preparative LC/MS purification; LC/MS purity 98%, t_R = 1.23 min. ^{1}H NMR (300 MHz, $CDCl_3$/MeOD): δ 2.69–2.70 (m, 2H), 3.30 (br s, 2H), 3.79 (d, 2H, J = 3.1 Hz), 6.10 (s, 1H), 7.07–7.12 (m, 2H), 7.27 (dd, J = 8.7 Hz, J = 2.1 Hz, 1H), 7.53 (s, 1H), 7.62 (d, 1H, J = 2.1 Hz), 7.82–7.87 (m, 3H). MS calcd for $[M+H]^+$: $C_{19}H_{17}ClFN_2O_2S$ *m/z* 391.1, found 391.2.

4-Fluoro-N-[3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indol-5-yl]benzenesulfonamide (11a)

Yield: 17 mg (40% isolated yield) as a yellow oil following preparative LC/MS purification; LC/MS purity 100%, t_R = 1.05 min. ^{1}H NMR (300 MHz, acetone-d_6): δ 2.87–2.9 (m, 2H), 3.57–3.61 (m, 2H), 3.62 (br s, 1H), 4.03–4.04 (m, 2H), 6.05–6.06 (m, 1H), 6.95 (dd, J = 6.6 Hz, J = 2 Hz, 1H), 7.22–7.29 (m, 2H), 7.34 (dd, J = 7.9 Hz. J = 0.5 Hz, 2H), 7.52 (s, 1H), 7.68 (dd J = 2 Hz, J = 0.5 Hz, 1H), 7.75–7.82 (m, 2H). MS calcd for $[M + H]^+$: $C_{19}H_{19}FN_3O_2S$ *m/z* 372.1, found 372.1.

N-[3-(Piperazin-1-yl)phenyl]benzenesulfonamide (15a)

Yield: 16 mg (37% isolated yield) as a yellow oil following preparative LC/MS purification; LC/MS purity 99%, t_R = 0.99 min. ^{1}H NMR (300 MHz, acetone-d_6): δ 2.8–2.84 (m, 4H), 3.29–3.46 (m, 4H), 6.7–6.77 (m, 2H), 6.88 (t, J = 2 Hz, 1H), 7.11 (t, J = 8 Hz, 1H), 7.5–7.56 (m, 2H), 7.57–7.63 (m, 1H), 7.8–7.86 (m, 2H). MS calcd for $[M + H]^+$: $C_{16}H_{20}N_3O_2S$ *m/z* 318.1 found 318.1.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.036.

References and notes

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