Non-Amide-Based Combinatorial Libraries Derived from *N*-Boc-Iminodiacetic Acid: Solution-Phase Synthesis of Piperazinone Libraries with Activity Against LEF-1/*β*-Catenin-Mediated Transcription

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Dedicated to *Albert Eschenmoser* on the occasion of his 75th birthday

The development of a solution-phase approach to the rapid, parallel synthesis of highly functionalized piperazinones in only four steps starting from *N*-Boc-iminodiacetic acid is detailed. The efforts represent the extension of the solution-phase synthesis of combinatorial libraries from *N*-Boc-iminodiacetic acid to non-amide-based libraries where simple liquid-liquid extractions are employed to purify all reaction products. This methodology was applied to the synthesis of a diverse 150-member library with substituents in three positions of the piperazinone core. Screening results from a luciferase reporter assay indicate that a number of library members are novel repressors of LEF-1/*β*-catenin-mediated transcription, and may be effective agents against colorectal tumors. Two secondary libraries (100 members each) designed from these lead structures were synthesized and screened, providing additional active agents and insight into key structure-activity relationships in the series. These compounds represent only the second class of small molecules which repress transcription of reporter genes containing LEF-1 responsive elements, and the first group not based on DNA minor-groove-binding agents.

Introduction. – Combinatorial libraries have emerged as a leading source of compounds for biological screens. Originally described for peptides and related oligomers [1][2], combinatorial chemistry has focused on the generation of libraries of small organic molecules [3] structurally related to traditional pharmaceuticals [4]. In recent efforts, we have described the development of multi-step solution-phase techniques for the preparation of combinatorial libraries, whose technically non-demanding nature and unlimited scale provide attractive alternatives to more traditional solid-phase methods. In these studies, templates such as *N*-Boc-iminodiacetic acid anhydride (**1**) and related anhydrides have been exploited through sequential amide couplings for the rapid parallel synthesis of individual compounds and combinatorial mixtures [5][6]. Recently, we extended this approach by introducing diversity through the formation of C,C bonds *via* olefin metathesis [7], *Stille* [8] and biaryl [9] coupling reactions. In all cases, reaction and workup conditions were designed that permitted the isolation and purification of products through simple liquid-liquid or liquid-solid extractions.

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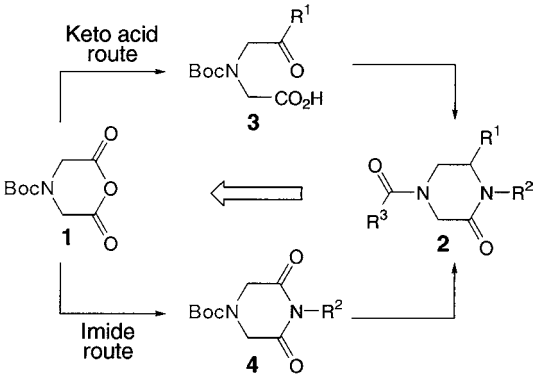
Herein, we describe an important extension of this solution-phase methodology to the preparation of non-amide-based libraries from *N*-Boc-iminodiacetic acid with the large scale, parallel synthesis of a prototypical 150-member library of 4-acyl-1,6-dialkyl-piperazin-2-ones **2**. Combinatorial piperazinone ('ketopiperazine') libraries have previously been described, although with different substitution patterns [10]. Substituted piperazinones have been used in the generation of conformationally restrained peptidomimetics [11], and several have been identified that have potent activity in a variety of biological assays [12]. Screening results have revealed that a number of compounds from our initial piperazinone library and subsequent secondary libraries are active in a luciferase reporter assay measuring transcription from lymphoid-enhancer binding factor (LEF-1) responsive elements. A majority of colorectal tumors contain *adenomatous polyposis coli* (APC) mutations, which result in nuclear accumulation of β-catenin, which binds to and activates transcription factors including LEF-1 [13]. The resulting upregulated and aberrant gene expression is a key step in the development of colorectal adenomas, and the discovery of compounds that can disrupt LEF-1/β-catenin-mediated transcription may lead to novel therapeutics for colon cancer.

Developmental Studies. The route to the piperazinone core was anticipated to begin with introduction of the R^1 substituent by addition of a carbon nucleophile to the iminodiacetic acid template[2]), resulting in keto acid **3** (*Scheme 1*). The direct addition of organometallic reagents to anhydride **1** was first investigated with several classes of reagents including BuLi, Et_2Zn, α-bromoacetate with Zn/Cu couple in DMF [15] and malonic acid/Et_3N [16]. By and large, the efforts were unsuccessful, giving complex mixtures containing undesired side-products (*Scheme 2*).

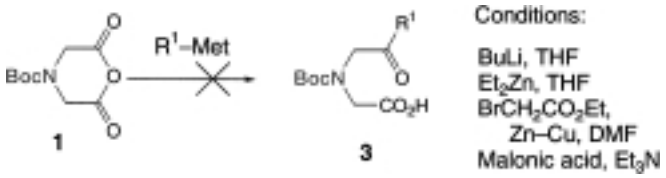
Scheme 1. *Two Routes Explored for the Synthesis of a 4-Acyl-1,6-dialkyl Piperazinone Library from* N-*Boc-Iminodiacetic Acid Anhydride*



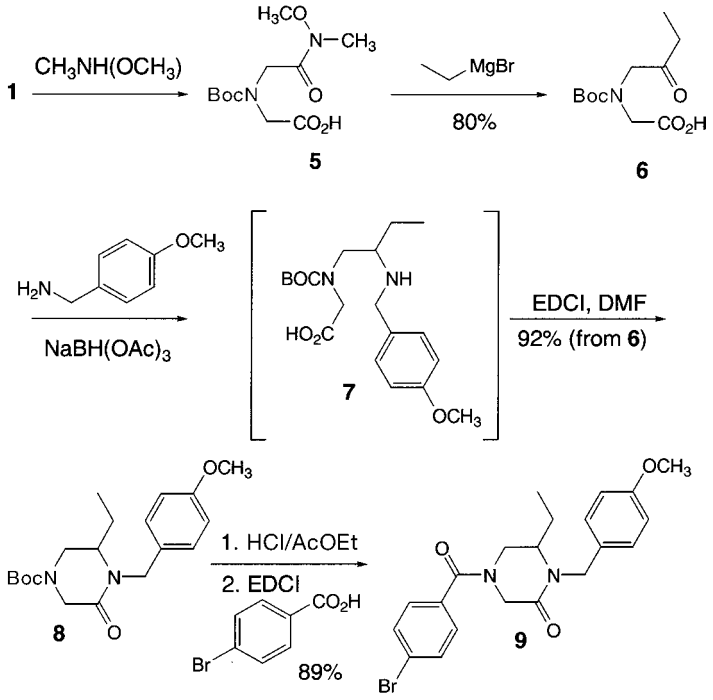
The approach was improved by introducing the *Weinreb* amide **5** [17] as an intermediate (*Scheme 3*). Addition of *N*-methoxy-*N*-methylamine hydrochloride to **1**

[2]) *N*-Boc-Iminodiacetic acid anhydride (**1**) is typically generated *in situ* from the readily available dicarboxylic acid (see [5][6]). Alternatively, it can be isolated and stored for subsequent reactions (*cf.* [14]).

Scheme 2



Scheme 3



in the presence of $EtN(i\text{-}Pr)_2$ provided **5**. The R^1 substituent could then be introduced by addition of a *Grignard* reagent. The developmental model reaction with EtMgBr required reaction temperatures of $0-25°$ for more than 1 h to achieve complete conversion, but no by-products from over-addition were observed. Isolation and purification of the keto acid product **6** was accomplished by a phase-switch extractive workup. After quenching, the reaction mixture was partitioned between Et_2O and 2M aqueous NaOH. The Et_2O phase was discarded, removing neutral organic impurities, and the desired keto-acid product was then liberated from the aqueous phase by acidification (HCl) and extraction into Et_2O. The isolated yield was 80% and the product **6** was pure by TLC and ^{1}H-NMR analysis.

The second substituent (R^2) in our developmental system was introduced by reductive amination of the ketone. Compound **6** was found to be an excellent

substrate[3]), and reaction with 4-methoxybenzylamine in the presence of sodium triacetoxyborohydride ($NaBH(OAc)_3$)[4]) and AcOH proceeded smoothly, yielding the crude amino acid **7** after evaporation of the solvent. This unpurified product was directly cyclized by treatment with 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI) to form the *N*-Boc-piperazinone **8**. Although obtained in good yield (92%), the product **8** was contaminated with neutral by-products that necessitated purification by flash chromatography. Alternative reaction conditions were developed that facilitated product isolation and purification by simple liquid-liquid extractions. The major contaminant in product **8** was *N*-(4-methoxybenzyl)acetamide, derived from the EDCI coupling of unreacted amine and AcOH remaining from the reductive amination step. Since we planned to perform this sequence (reductive amination and cyclization) without purification of the amino-acid intermediate, we developed conditions to ensure that any unreacted starting materials or reagents from the reductive amination would not lead to inseparable by-products under the conditions of the cyclization step. Several reaction stoichiometries were investigated; the optimal one had a ratio of amine (0.65 equiv.) to keto acid (1 equiv.) with a slight excess of reducing and coupling agents. When **6** was submitted to these conditions without purification of intermediate **7**, a simple acid/base extractive workup after the cyclization reaction provided piperazinone **8** (92% yield, >95% pure), identical (TLC, ^{1}H-NMR) to material purified by flash chromatography.

The third subunit (R^3) in our developmental system was incorporated by a sequential deprotection/acylation sequence of the Boc-protected secondary amine. Thus, treatment of **8** with HCl/AcOEt followed by coupling with 4-bromobenzoic acid effected by EDCI afforded the final product **9** in 89% yield and excellent purity (^{1}H-NMR) after extractive workup.

Additional methods for the modification of the piperazinone secondary amine were explored for introduction of the final (R^3) substituent. Two alkylation reactions were developed based on piperazinone **10**, prepared from **6** using 3-(trifluoromethyl)benzylamine under the above conditions. Thus, *N*-Boc deprotection (HCl/AcOEt) and treatment of the resulting crude HCl salt with $PhCH_2Br$ (1.05 equiv.) and $EtN(i\text{-}Pr)_2$ (1.3 equiv.) in DMF at 25° for 17 h provided the crude reaction product. After acid/base extractive workup, the desired *N*-alkylated product **11** was isolated in 96% yield and excellent purity (^{1}H-NMR, >95% pure) (*Scheme 4*). Reductive-amination conditions were also investigated. *N*-Boc deprotection (HCl/AcOEt) followed by treatment of the free amine with 4-methoxybenzaldehyde (1.05 equiv.), $NaBH_3CN$ (2.6 equiv.), and AcOH (2.0 equiv.) in 1,2-dichloroethane at 25° for 40 h provided **12**. In this case, a small amount (<20%) of 4-methoxybenzyl alcohol by-product remained after the extractive workup. These model reactions demonstrated that alkylation of the piperazinone secondary amine is a useful alternative to amide couplings for the

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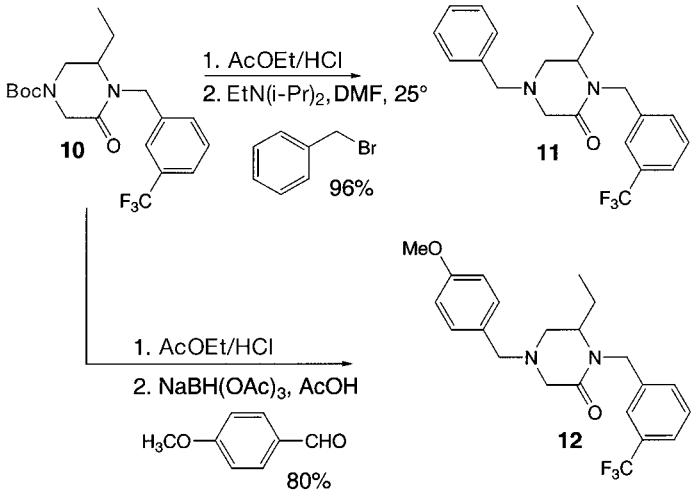
[3]) The 4-methylphenyl ketone (synthesized analogously from **5** by reaction with toluoyl magnesium bromide) failed to react with 4-methoxybenzylamine in the presence of $NaBH_3CN$ or $NaB(OAc)_3H$ presumably because of steric and/or electronic factors. We, therefore, limited our library to alkyl substituents at the R^1 position.

[4]) $NaBH_3CN$ was also effective for this transformation, although the reactions were more sluggish. Since the cyanoborohydride reagent itself and the resulting aqueous waste from the reaction workup are toxic, $NaBH(OAc)_3$ [18] was adopted for the library synthesis.

introduction of the final (R^3) diversity subunit, although we limited our first prototypical library synthesis to the latter.

Scheme 4

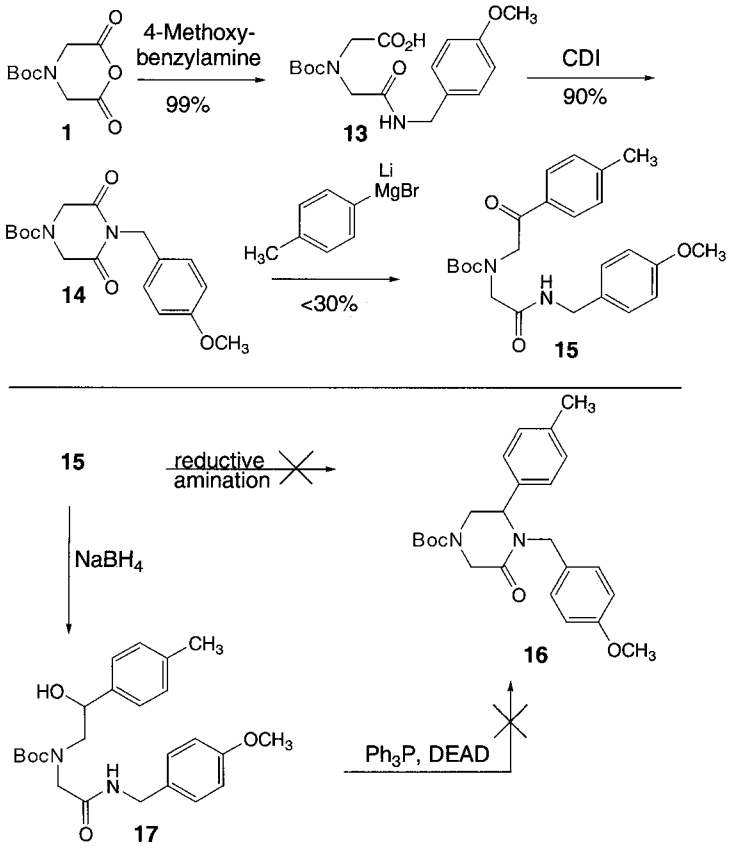


A briefly explored alternative proceeded through the symmetrical piperazine-2,6-dione **4** (*Scheme 1*). Reaction conditions were developed for the cyclization of monoamide **13**, obtained from the reaction of 4-methoxybenzylamine with **1**, to give imide **14** (*Scheme 5*). Several dehydrating reagents were investigated, including $(CF_3CO)_2O$, Ac_2O, and EDCI. The most effective reagent was 1,1′-carbonyldiimidazole (CDI; 4 equiv.), which provided **14** in 90% yield and excellent purity after a simple acid/base extractive workup. However, the yield of the addition of *Grignard* and organolithium reagents to **14** to provide the desired product (*e.g.*, **15**) was typically $<30\%$. In addition, initial attempts at subsequent cyclization, either directly *via* intramolecular reductive amination, or by reduction to alcohol **17** and subsequent *Mitsunobu* cyclization with Ph_3P and diethyl azodicarboxylate (DEAD) to form piperazinone **16** were not encouraging.

Library Synthesis. The reaction sequence and conditions optimized in our developmental system were applied to the synthesis of a 150-member piperazinone library. From commercially available materials, three organomagnesium reagents were selected for the R^1 subunit (**A1**–**A3**), five primary amines for the R^2 subunit (**B1**–**B5**), and ten aromatic carboxylic acids were chosen for the R^3 position (**C1**–**C10**; see *Fig. 1*). Compound **5** was used as the starting point for the library synthesis, and addition of ethyl, benzyl, and phenethyl *Grignard* reagents provided large quantities (>8 g) of **6**, **18**, and **19**, respectively, in excellent purity after the phase-switch extractive workup (*Scheme 6*).

Compounds **6**, **18**, and **19** were each divided into five equal portions and submitted to the reductive amination/intramolecular cyclization sequence with amines **B1**–**B5**. This afforded the desired *N*-Boc-protected piperazinones (**8**, **10**, **20**–**32**) in excellent

Scheme 5



yields (average 97%) after acid/base extractive workup[5]). Each of **8**, **10**, **20**–**32** were divided into ten equal portions and deprotected (HCl/AcOEt). The resulting crude HCl salts were directly coupled (EDCI) with each of the ten carboxylic acids **C1**–**C10**. The products were isolated by acid/base liquid-liquid extractions, which effectively removed all reagents, unreacted starting materials, and reaction by-products, providing the library of 150 individual compounds (**33**). The yields for these reactions were good-to-excellent (*Table 1*), and 30 representative samples were characterized by ^{1}H-NMR, HR-MS, and IR (matrix characterization). In each case, the desired acylated piperazinone was identified in excellent purity.

Repression of Transcription from LEF-1 Response Elements. – The amount of each isolated product (typically 80–100 mg) is ideal for depository libraries, which are tested

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[5]) To establish the integrity of intermediates **8**, **10**, and **20**–**32**, portions of the crude material of one series (**23**–**27**) were purified by flash chromatography. The purity of the intermediates was determined from the ratio of the masses of the materials isolated from the flash column to the masses of the crude reaction products. By this method, an average purity of 86% was established.

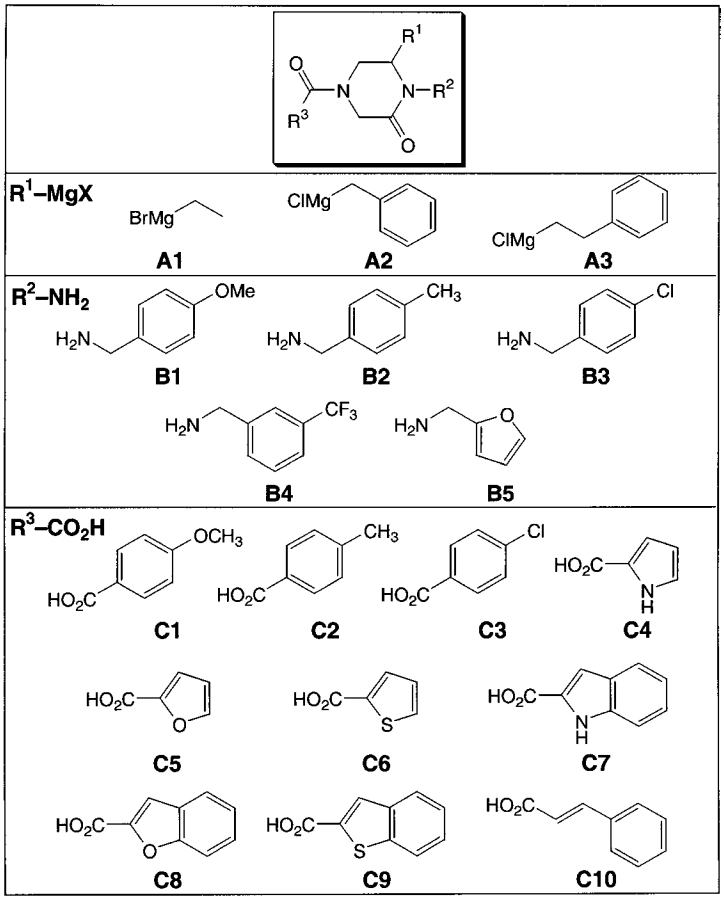

Fig. 1. *Structures of R^1 subunits* **A1**–**A3**, *R^2 subunits* **B1**–**B5**, *and R^3 subunits* **C1**–**C10**

in several biological screens over many years, and our initial 150-member piperazinone library is currently being examined in a number of assays that target protein-protein interactions. Several leads were identified from the screening of this library against LEF-1/β-catenin-mediated transcription in a colon-cancer cell line (SW480). In a luciferase assay based on a reporter containing 4 copies of the LEF-1 binding site upstream from the c-*fos* promoter (known as TOPFLASH) [19], several compounds (10 μM concentration) significantly repressed transcription (*Table 2*). Sixteen selected compounds were then retested by repeating the assay with TOPFLASH and a similar reporter where the LEF-1 binding sites in front of the promoter were mutated and inactive (FOPFLASH [19], *Fig. 2*). Several of these agents (*e.g.*, **33**: **A1B1C8**, **A1B2C3**, **A1B2C8**, **A1B3C6**, **A1B3C9**, and **A3B4C6**, see *Table 3*) inhibited transcription as much as five-fold and displayed an approximately twofold greater repression of transcription in TOPFLASH than in the FOPFLASH system, demonstrating their selectivity. These agents represent, to the best of our knowledge, only the second class of small-molecule compounds that repress transcription from LEF-1

Scheme 6

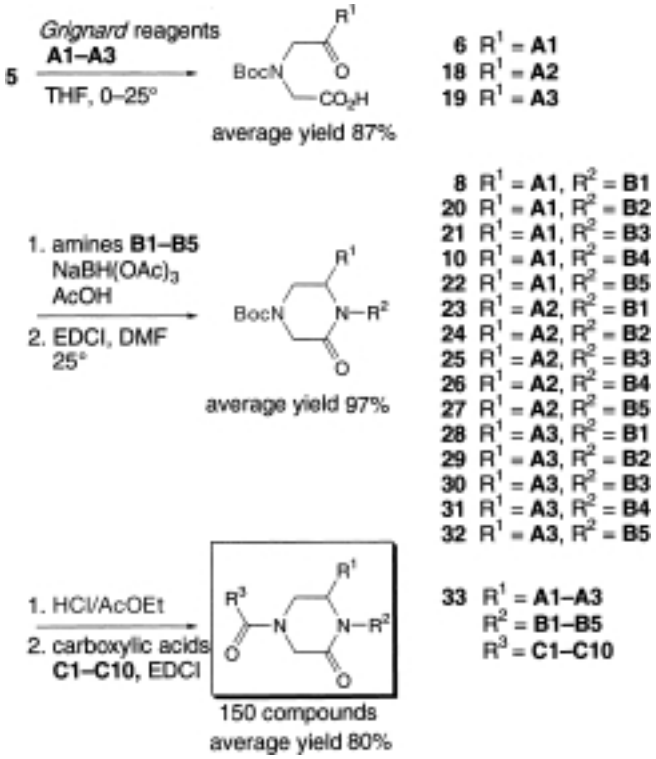

Table 1. *Yields* [%] *for the Final Coupling Step for Library* **33**

33	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
A1B1	76	79	82	71	71	61	81	71	71	74
A1B2	83	77	77	73	76	85	78	72	71	81
A1B3	91	93	77	79	82	91	85	74	86	93
A1B4	91	87	77	79	84	80	83	74	81	87
A1B5	77	77	81	67	69	77	85	71	74	80
A2B1	83	82	94	79	83	82	100	90	91	98
A2B2	79	88	80	80	80	82	70	49	79	90
A2B3	95	89	87	81	87	89	87	86	93	93
A2B4	59	59	65	66	69	62	59	69	68	56
A2B5	78	77	75	76	71	76	62	69	76	87
A3B1	84	83	78	70	77	84	57	73	74	87
A3B2	84	80	74	71	76	84	81	67	69	90
A3B3	86	83	77	75	82	85	81	73	79	88
A3B4	85	85	80	70	79	83	81	73	77	87
A3B5	72	86	80	74	75	82	86	66	73	88
	Average yield 80%									

responsive elements and the first class that is not based on DNA minor-groove-binding agents[6]).

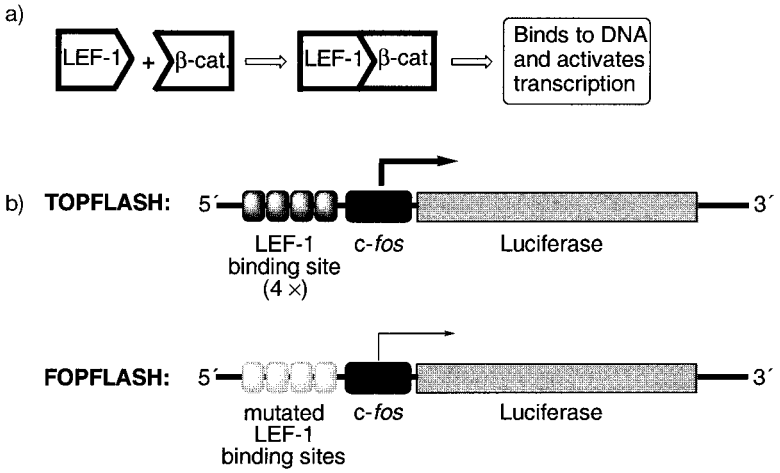

Fig. 2. *Schematic representation of LEF-1 activation of transcription. a*) *β*-Catenin binds to LEF-1 and activates transcription from LEF-1 responsive elements. *b*) In both the TOPFLASH and FOPFLASH reporter systems, expression of the luciferase gene (gray box) is driven by the c-*fos* minimal promoter (black box). TOPFLASH contains four copies of the LEF-1 binding site (CCTTTGATC) upstream from the promoter that augment transcription, whereas FOPFLASH contains mutated, inactive LEF-1 binding sites (CCTTTGGCC). The level of transcription is determined by measuring luciferase activity (luminescence).

Table 2. *Fold Repression of Transcription of a Luciferase Reporter with LEF-1 Binding Sites in the Promoter Region* (TOPFLASH)[a])

33	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
A1B1	1.14	1.49	2.13	1.06	1.19	1.64	2.00	3.85	1.52	1.61
A1B2	1.72	1.92	3.70	1.14	1.52	2.63	1.75	3.45	4.76	2.38
A1B3	1.89	1.92	2.94	1.96	1.82	2.94	1.45	2.50	4.17	2.00
A1B4	1.33	1.75	2.17	1.10	1.08	2.08	1.09	1.85	2.00	1.69
A1B5	0.72	1.20	0.63	0.83	0.89	1.32	1.25	1.45	1.15	0.79
A2B1	1.00	1.04	1.20	0.85	1.33	0.72	1.61	1.33	1.19	1.89
A2B2	1.32	1.32	1.41	1.03	1.41	0.97	0.86	1.28	2.17	1.27
A2B3	1.67	1.03	1.54	0.90	1.05	1.61	1.08	1.11	1.56	1.56
A2B4	2.04	1.20	2.50	1.04	1.45	1.82	1.39	1.67	1.49	1.89
A2B5	1.10	1.82	1.56	1.54	0.97	1.45	1.33	2.22	1.47	2.44
A3B1	1.15	1.28	0.84	1.27	1.02	1.27	1.30	1.39	1.30	1.47
A3B2	1.52	1.61	1.12	1.14	1.14	1.02	1.02	1.10	1.59	1.20
A3B3	1.11	1.16	1.25	1.61	1.54	1.23	0.88	1.10	1.47	1.52
A3B4	1.37	1.64	1.89	1.64	1.92	3.57	0.68	1.23	1.04	1.61
A3B5	1.10	1.19	1.35	1.02	1.23	1.14	1.10	1.19	1.47	0.68

[a]) All compounds were tested at 10 μM concentration. Inhibition of transcription was determined by luciferase activity.

6) Recently, heterocyclic polyamides that bind to the minor groove of DNA have been shown to repress transcription of genes with LEF-1 responsive elements in the promoter [20].

Table 3. *Ratio of Fold Repression of Transcription with LEF-1* (TOPFLASH) *and Mutated, Inactive LEF-1* (FOPFLASH) *Binding Sites in the Luciferase Promoter Region*[a])

33	TOPFLASH/ FOPFLASH Repression ratio	**33**	TOPFLASH/ FOPFLASH Repression ratio
A1B1C8	2.00	**A1B4C6**	1.07
A1B2C3	2.16	**A2B1C10**	1.23
A1B2C8	1.67	**A2B2C9**	1.40
A1B2C9	1.50	**A2B4C1**	1.17
A1B3C3	1.44	**A2B4C3**	1.00
A1B3C6	1.88	**A2B5C8**	1.06
A1B3C9	2.07	**A2B5C10**	1.26
A1B4C2	1.38	**A3B4C6**	2.22

[a]) All compounds were tested at 10 μM concentration. Inhibition of transcription was determined by luciferase activity. See text and *Fig. 2* for explanation of TOPFLASH and FOPFLASH reporter systems.

Secondary Library Synthesis and Screening. The screening results in *Tables 2* and *3* reveal that the majority of active compounds from the library contain the ethyl subunit (**A1**) in the R^1 position, and that 4-methyl- and 4-chlorobenzylamines (**B2** and **B3**) were the most active among the R^2 substitutions. Since each of these subunits was tested only in combination with a limited number of R^3 subunits (**C1**–**C10**) in the initial library, secondary libraries containing **A1B2** and **A1B3** were prepared containing increased diversity at position R^3. The synthesis of these libraries required only one step from archived samples of compounds **20** and **21**, following the same synthetic strategy as in the original 150-member library. Each of **20** and **21** was subjected to *N*-Boc deprotection (HCl/AcOEt), and reacted with **C11**–**C110** (**20**) or **C111**–**C210** (**21**) to provide two 100-member libraries **33**, **A1B2C11**–**110**, and **33**, **A1B3C111**–**C210** (*Figs. 3* and *4*, and *Scheme 7*). Each library product was purified by acid/base liquid-liquid extractions, providing the final library members in $\geq$90% purity in good to excellent conversions (*Table 4*). As in the initial library synthesis, the majority of the new R^3 subunits coupled to **20** and **21** were carboxylic acids. However, sulfonyl chlorides, chloroformates, and isocyanates were also included, producing sulfonamide, carbamate, and urea linkages, respectively, in the final library products. The inclusion of the latter functional groups demonstrates the diversity of chemistry achievable by solution-phase techniques.

Results from the screening of **33**, **A1B2C11**–**C110**, and **33**, **A1B3C111**–**C210**, in the TOPFLASH reporter assay are presented in *Figs. 3* and *4*. Although no increase in repression over the original library was observed for these compounds, the nine most active in the series were tested in the FOPFLASH assay (*Table 5*), where they

Table 4. *Average Yields for the Synthesis of the Secondary Libraries* (**33**, **A1B2C11**–**110** and **33**, **A1B2C111**–**210**) *from* N-*Boc-Piperazinones* **20** *and* **21**

Reagent type	RCO_2H (**C11**–**C95**) (**C111**–**C196**)	ROCOCl (**C96**–**C100**) (**C197**–**C201**)	RSO_2Cl (**C101**–**C105**) (**C202**–**C206**)	RNCO (**C106**–**C110**) (**C207**–**C210**)
20 (**A1B2**)	54%	80%	66%	86%
21 (**A1B3**)	70%	90%	91%	95%

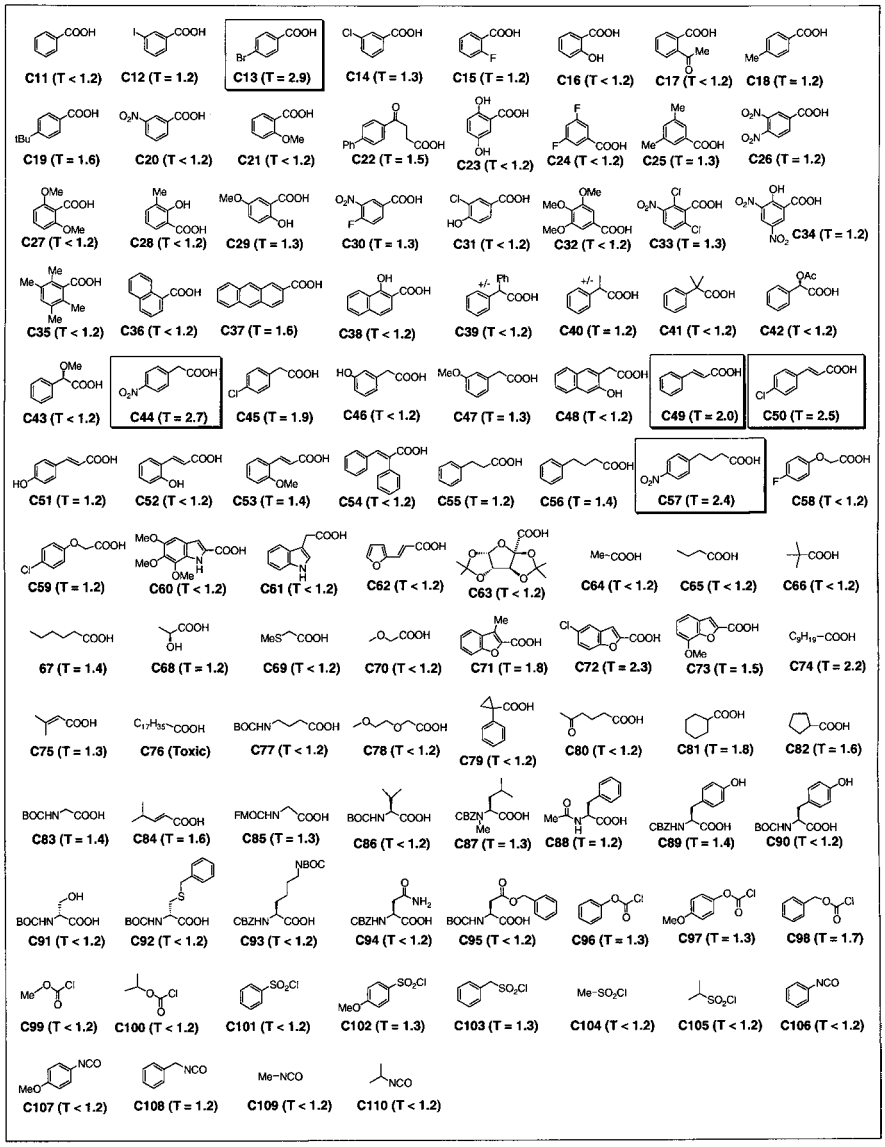

Fig. 3. *Structures of the 100 R^3 subunits* (**C11**–**C110**) *coupled to* **20**. Results of the TOPFLASH reporter assay (fold repression of transcription) are given in parentheses.

displayed selectivity for repressing LEF-1-mediated transcription (TOPFLASH/FOPFLASH transcription ratios of 1.6–2.3). Analysis of the screening results (*Figs. 3* and *4*) for entire set of compounds also reveals insight into structure-activity relationships (SAR) for the R^3 substitutions and provides several general observations:

– Carboxamide > carbamate > sulfonamide > urea linkages

– A hydrophobic or aromatic group is required

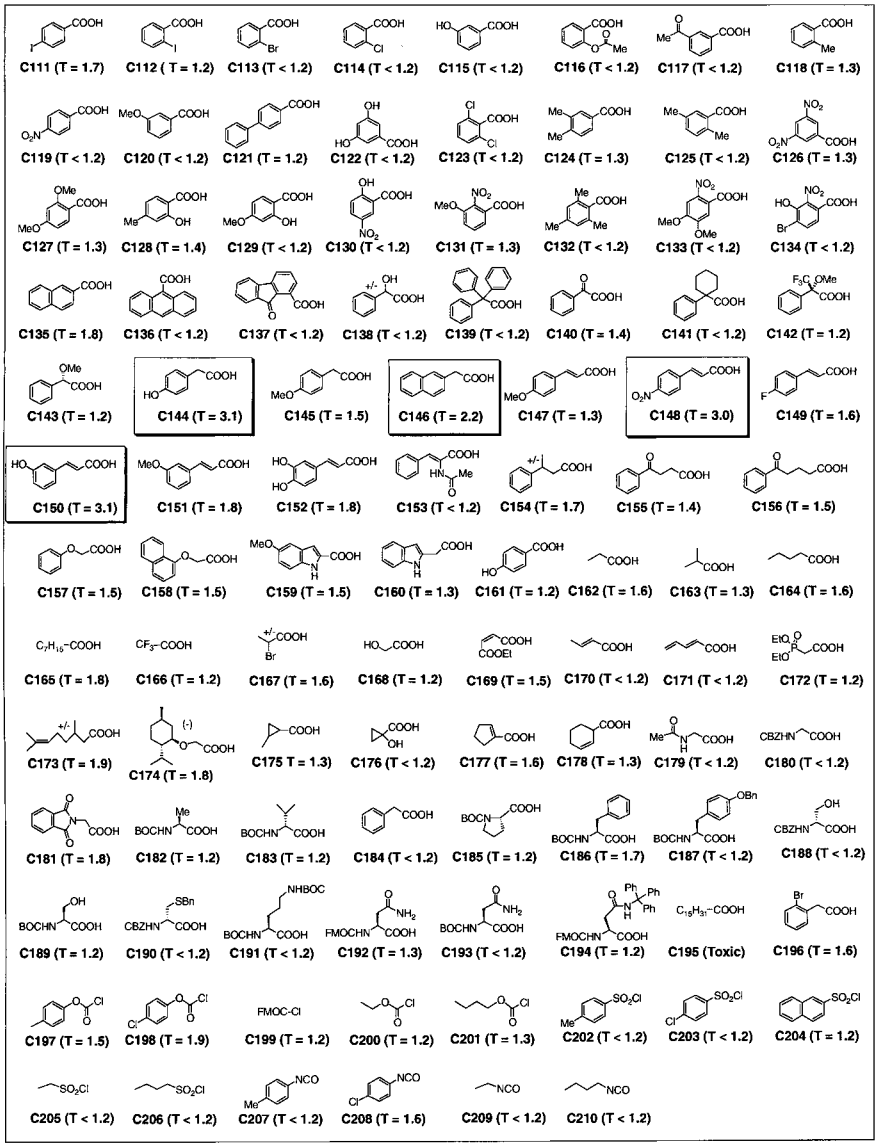

Fig. 4. *Structures of the 100 R^3 subunits* (**C111 – C210**) *coupled to* **21**. Results of the TOPFLASH reporter assay (fold repression of transcription) are given in parentheses.

- For aromatic substituents: phenyl > naphthyl > anthracyl, fluorenyl
- Aryl substitution: NO_2, Cl, Br, OH > I, Me, OMe > F, Acetyl
- For phenyl substitutions: *para* > *meta* > *ortho*; No. of substitutions: 1 > 2 > 3, 4
- Spacer length between the piperazinone N(4) and phenyl ring: 3 atoms (cinnamyl) > 2 atoms (phenylacetyl) > 1 atom (benzoyl)
- Hydrophilic subunits should be avoided.

Scheme 7. *Synthesis of Two Secondary Piperazinone Libraries Based on Initial Screening Results.* See text and *Table 4* for details.

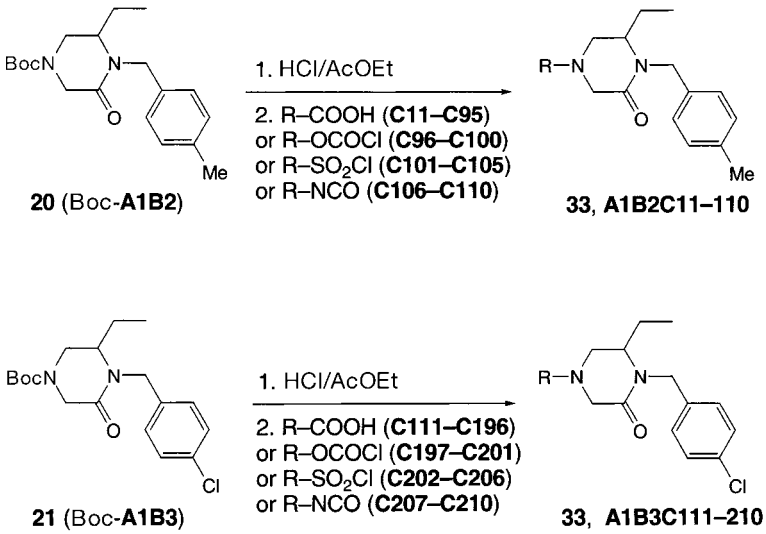

Table 5. *Biological Activity of the Most Effective Compounds from the Secondary Libraries*[a])

33	Fold repression on TOPFLASH	TOPFLASH/FOPFLASH repression ratio
A1B2C13	2.7	1.8
A1B2C44	2.9	1.9
A1B2C49	2.3	2.0
A1B2C50	3.0	2.3
A1B2C57	2.5	1.6
A1B3C144	3.0	1.8
A1B3C146	2.2	1.7
A1B3C148	2.7	1.7
A1B3C150	2.7	1.6

[a]) All compounds were tested at 10 μM concentration. Inhibition of transcription was determined by luciferase activity. See text and *Fig. 2* for an explanation of TOPFLASH and FOPFLASH reporter systems.

The syntheses of additional secondary libraries to further explore the effects of increased diversity at positions R^1 and R^2 are in progress. Studies are also underway to further define the structural features contributing to transcription inhibition, to determine the agents' cellular targets, and to measure their effect on the growth of colorectal tumors. These results will be disclosed in due course.

Conclusions. – A 150-member library of non-amide-based 4-acyl-1,6-dialkylpiperazinones was synthesized from *N*-Boc-iminodiacetic acid by solution-phase techniques. Simple liquid-liquid extractions provided pure reaction intermediates and final products in quantities sufficient (80 – 100 mg) for screening in a variety of biological assays, thus extending the solution-phase combinatorial methodology beyond amide-bond formation. Members of this library were found to have activity against LEF-1/β-

catenin-mediated transcription. Two secondary libraries (100 compounds each) based on further diversification of position 4 of the 1,6-dialkylpiperazinone core (R^3) provided additional active compounds and revealed structural requirements for the observed biological activity. Exploration of these novel leads as well as the results from subsequent syntheses and screens will be forthcoming.

Experimental Part

General. IR Spectra were obtained on KBr plates (film); in cm^{-1}. ^{1}H-NMR Spectra were recorded at 400 MHz; chemical shifts δ in ppm, coupling constants J in Hz. HR-MS was performed by the fast-atom-bombardment (FAB) technique with a 3-nitrobenzyl alcohol (NBA)/NaI matrix.

N-*[(*tert-*Butoxy)carbonyl]*-N-*[(methoxy)(methyl)carbamoylmethyl]glycine* (**5**). A soln. of *N*-Boc-iminodiacetic acid (**1**; 90 g, 390 mmol) in DMF (600 ml) was treated with EDCI (89 g, 460 mmol) in several portions at 0° and then warmed to 25°, and stirred for 1 h. The mixture was cooled to 0° and treated dropwise with a premixed soln. of *N*-methoxymethylamine hydrochloride (45 g, 460 mmol) and $EtN(i\text{-}Pr)_2$ (80 ml, 460 mmol) in DMF (200 ml), and stirred for an additional 10 h at 25°. The mixture was poured into a flask containing ice (1.0 kg) and 10% aq. HCl (1.0 l) and extracted wtih AcOEt (2 × 1.0 l). The org. phases were combined and washed with 10% aq. HCl (2 × 1.0 l) and sat. aq. NaCl soln. (1.0 l), dried (Na_2SO_4), and evaporated *in vacuo*. The resulting solid was washed with Et_2O (250 ml) and filtered to afford **5** (42.02 g, 39%). White powder: M.p. 92–94°. IR: 2998, 2943, 2707, 2605, 1754, 1702, 1625, 1461, 1446, 1390, 1369, 1246, 1159, 1133, 1000, 969, 933, 897, 856, 795, 769. ^{1}H-NMR ((D_6)DMSO): 4.18 (*s*, 1 H); 4.14 (*s*, 1 H); 3.90 (*s*, 1 H); 3.87 (*s*, 1 H); 3.69 (*s*, 1.5 H); 3.67 (*s*, 1.5 H); 3.10 (*s*, 1.5 H); 3.09 (*s*, 1.5 H); 1.35 (*s*, 4.5 H); 1.34 (*s*, 4.5 H). HR-MS: 277.1398 ($[M+H]^+$, $C_9H_{15}NO_6^+$; calc. 277.1400).

General Procedure for the First Diversification: N-*[(*tert-*Butoxy)carbonyl]*-N-*(2-oxobutyl)glycine* (**6**). A soln. of **5** (9.96 g, 36.1 mmol) in THF (200 ml) was cooled to 0° and treated with EtMgBr (1.0M soln. in THF, 79 ml, 79 mmol) dropwise *via* syringe. The mixture was stirred at 25° for 1 h, and then cooled to 0° and quenched by the slow addition of sat. aq. NH_4Cl (100 ml) soln. and H_2O (100 ml). After stirring for 3 h at 25°, Et_2O (500 ml) was added, and the mixture was extracted with 2M aq. NaOH (300 ml). The aq. layer was acidified by the addition of conc. aq. HCl (30 ml) at 0° and then twice extracted with Et_2O (1000 ml and 500 ml). The org. phases were combined, washed with sat. aq. NaCl soln. (300 ml), dried (Na_2SO_4), and evaporated to give **6** (8.24 g, 93%). Pale yellow oil. IR: 2979, 2940, 1708, 1698, 1650, 1642, 1632, 1478, 1454, 1394, 1369, 1251, 1165, 1042, 901, 877, 858, 778. ^{1}H-NMR ((D_6)DMSO): 4.06 (*s*, 1 H); 4.03 (*s*, 1 H); 3.87 (*s*, 1 H); 3.83 (*s*, 1 H); 2.40 (*q*, J = 7.2, 1 H); 2.38 (*q*, J = 7.2, 1 H); 1.35 (*s*, 4.5 H); 1.32 (*s*, 4.5 H); 0.94 (*t*, J = 7.2, 1.5 H); 0.92 (*t*, J = 7.2, 1.5 H). HR-MS: 268.1298 ($[M+Na]^+$, $C_{11}H_{19}NO_5^+$; calc. 268.1290).

N-*[(*tert-*Butoxy)carbonyl]*-N-*(2-oxo-3-phenylpropyl)glycine* (**18**). Yield 89%. IR: 2978, 2937, 1726, 1700, 1496, 1475, 1449, 1396, 1370, 1250, 1156, 1067, 962, 905, 858, 758, 701, 659. ^{1}H-NMR ($CDCl_3$): 7.37–7.24 (*m*, 3 H); 7.23–7.16 (*m*, 2 H); 4.20 (*m*, 1.33 H); 4.10 (*m*, 0.67 H); 3.95 (*s*, 0.67 H); 3.82 (*s*, 1.33 H); 3.80 (*s*, 1.33 H); 3.71 (*s*, 0.67 H); 1.42 (*s*, 6 H); 1.33 (*s*, 3 H). HR-MS: 308.1506 ($[M+H]^+$, $C_{16}H_{21}NO_5^+$; calc. 308.1498).

N-*[(*tert-*Butoxy)carbonyl]*-N-*(2-oxo-4-phenylbutyl)glycine* (**19**). Yield 79%. IR: 2974, 2923, 1728, 1697, 1456, 1390, 1369, 1246, 1154, 907, 851, 749, 703. ^{1}H-NMR ($CDCl_3$): 7.31–7.09 (*m*, 5 H); 4.13–3.75 (*m*, 4 H); 2.99–2.66 (*m*, 4 H); 1.44 (*s*, 6 H); 1.35 (*s*, 3 H). HR-MS: 344.1485 ($[M+Na]^+$, $C_{17}H_{23}NO_5^+$; calc. 344.1474).

General Procedure for the Second Diversification and Cyclization to the N-*Boc-Piperazinone: 4-[(*tert-*Butoxy)carbonyl]-6-ethyl-1-[(4-methoxyphenyl)methyl]piperazin-2-one* (**8**). A stirred soln. of **6** (1.70 g, 6.92 mmol) in 1,2-dichloroethane (35 ml) was treated with 4-methoxybenzylamine (617 mg, 4.50 mmol), AcOH (0.40 ml, 6.9 mmol), and $NaBH(OAc)_3$ (1.91 g, 8.99 mmol), and the resulting suspension was stirred at 25° for 16 h. The solvent was removed under reduced pressure, and the residue was dissolved in DMF (30 ml) and treated with EDCI (1.33 g, 6.92 mmol), and stirred at 25° for 17 h. The mixture was extracted with AcOEt (150 ml) and washed with 10% aq. HCl (4 × 30 ml), sat. aq. $NaHCO_3$ (4 × 30 ml), and sat. aq. NaCl soln. (30 ml), dried (Mg_2SO_4), and evaporated to provide **8** (1.43 g, 92%). Pale yellow oil. IR: 2974, 1690, 1658, 1642, 1510, 1478, 1461, 1425, 1414, 1366, 1324, 1292, 1244, 1175, 1132, 1037, 994, 893. ^{1}H-NMR ($CDCl_3$): 7.15 (*d*, J = 8.5, 2 H); 6.83 (*d*, J = 8.5, 2 H); 5.30 (*d*, J = 14.6, 1 H); 4.52–4.25 (*m*, 1 H); 4.15–3.97 (*m*, 1 H); 3.94–3.81 (*m*, 2 H); 3.78 (*s*, 3 H); 3.14–2.83 (*m*, 2 H); 1.54-1.36 (*m*, 2 H); 1.44 (*s*, 9 H); 0.90 (*t*, J = 7.6, 3 H). HR-MS: 349.2120 ($[M+H]^+$, $C_{19}H_{28}N_2NO_4^+$; calc. 349.2127).

*4-[(*tert-*Butoxy)carbonyl]-6-ethyl-1-{[3-(trifluoromethyl)phenyl]methyl}piperazin-2-one* (**10**). Yield 100%. IR: 2974, 2932, 1695, 1653, 1637, 1419, 1366, 1324, 1292, 1244, 1164, 1127, 1074, 1000, 893, 803, 766. ^{1}H-NMR ($CDCl_3$): 7.57–7.49 (*m*, 1 H); 7.48–7.38 (*m*, H); 5.33 (*d*, *J* = 15.1, 1 H); 4.64–4.27 (*m*, 1 H); 4.21–3.78 (*m*, 2 H); 4.00 (*d*, *J* = 15.1, 1 H); 1.59–1.37 (*m*, 2 H); 1.45 (*s*, 9 H); 0.95 (*t*, *J* = 7.6). HR-MS: 387.1904 ($[M+H]^+$, $C_{19}H_{25}F_3N_2O_3^+$; calc. 387.1896).

*4-[(*tert-*Butoxy)carbonyl]-6-ethyl-1-[(4-methylphenyl)methyl]piperazin-2-one* (**20**). Yield 91%, based on the amine. IR: 2974, 2932, 1695, 1653, 1462, 1419, 1366, 1324, 1286, 1244, 1164, 1138, 994, 893. ^{1}H-NMR ($CDCl_3$): 7.10 (*s*, 4 H); 5.34 (*d*, *J* = 14.8, 1 H); 4.54–4.27 (*m*, 1 H); 4.16–3.95 (*m*, 1 H); 3.94–3.81 (*m*, 1 H); 3.82 (*d*, *J* = 14.8, 1 H); 3.13–2.87 (*m*, 2 H); 2.31 (*s*, 3 H); 1.56–1.39 (*m*, 2 H); 1.44 (*s*, 9 H); 0.90 (*t*, *J* = 7.6, 3 H). HR-MS: 333.2170 ($[M+H]^+$, $C_{19}H_{28}N_2O_3^+$; calc. 333.2178).

*4-[(*tert-*Butoxy)carbonyl]-1-[(4-chlorophenyl)methyl]-6-ethylpiperazin-2-one* (**21**). Yield 95%, based on the amine. IR: 2974, 2931, 2878, 1690, 1648, 1494, 1462, 1419, 1409, 1366, 1324, 1276, 1244, 1159, 1138, 1090, 1021, 994, 899. ^{1}H-NMR ($CDCl_3$): 7.27 (*d*, *J* = 8.4, 2 H); 7.15 (*d*, *J* = 8.4, 2 H); 5.26 (*d*, *J* = 14.8, 1 H); 4.54–4.27 (*m*, 1 H); 4.18–4.00 (*m*, 1 H); 3.96–3.77 (*m*, 1 H); 3.90 (*d*, *J* = 14.8, 1 H); 3.14–2.88 (*m*, 2 H); 1.56–1.35 (*m*, 2 H); 1.45 (*s*, 9 H); 0.91 (*t*, *J* = 7.3, 3 H). HR-MS: 353.1624 ($[M+H]^+$, $C_{18}H_{25}ClN_2O_3^+$; calc. 353.1632).

*4-[(*tert-*Butoxy)carbonyl]-6-ethyl-1-[(furan-2-yl)methyl]piperazin-2-one* (**22**). Yield 88%, based on the amine. IR: 2963, 2932, 2878, 1695, 1653, 1462, 1419, 1393, 1366, 1324, 1276, 1249, 1228, 1170, 1132, 1090, 1005, 989, 899, 856, 766, 734. ^{1}H-NMR ($CDCl_3$): 7.33 (br. *s*, 1 H); 6.30 (*dd*, *J* = 3, 2, 1 H); 6.26 (*d*, *J* = 3, 1 H); 5.12 (*d*, *J* = 15.4, 1 H); 4.49–4.21 (*m*, 1 H); 4.17–4.00 (*m*, 1 H); 4.06 (*d*, *J* = 15.4, 1 H); 3.91–3.71 (*m*, 1 H); 3.29–2.95 (*m*, 2 H); 1.54–1.36 (*m*, 2 H); 1.44 (*s*, 9 H); 0.93 (*t*, *J* = 7.3, 3 H). HR-MS: 309.1808 ($[M+H]^+$, $C_{16}H_{24}N_2O_4^+$; calc. 309.1814).

*4-[(*tert-*Butoxy)carbonyl]-1-[(4-methoxyphenyl)methyl]-6-(phenylmethyl)piperazin-2-one* (**23**). Yield 93%, based on the amine. IR: 2976, 2932, 1693, 1649, 1557, 1540, 1509, 1474, 1456, 1417, 1364, 1325, 1241, 1167, 1127, 1031, 960, 882. ^{1}H-NMR ($CDCl_3$): 7.33–7.07 (*m*, 7 H); 6.85 (*d*, *J* = 11.4, 2 H); 5.35 (*d*, *J* = 14.6, 1 H); 4.49–4.29 (*m*, 1 H); 4.10–3.71 (*m*, 2 H); 3.88 (*d*, *J* = 15, 1 H); 3.77 (*s*, 3 H); 3.50 (*m*, 1 H); 2.96–2.66 (*m*, 2 H); 2.71 (*dd*, *J* = 13.5, 10, 1 H); 1.53–1.40 (*m*, 9 H). HR-MS: 411.2272 ($[M+H]^+$, $C_{24}H_{30}N_2O_4^+$; calc. 411.2284).

*4-[(*tert-*Butoxy)carbonyl]-1-[(4-methylphenyl)methyl]-6-(phenylmethyl)piperazin-2-one* (**24**). Yield 100%, based on the amine. IR: 2974, 2930, 1697, 1649, 1474, 1456, 1417, 1364, 1325, 1285, 1246, 1167, 1132, 1031, 960, 925, 882, 750, 737, 702. ^{1}H-NMR ($CDCl_3$): 7.33–7.07 (*m*, 9 H); 5.38 (*d*, *J* = 14.6, 1 H); 4.48–4.28 (*m*, 1 H); 4.11–3.78 (*m*, 3 H); 3.34 (*m*, 1 H); 2.96–2.75 (*m*, 2 H); 2.71 (*dd*, *J* = 13.2, 9.7, 1 H); 2.31 (*s*, 3 H); 1.54–1.38 (*m*, 9 H). HR-MS: 395.2342 ($[M+H]^+$, $C_{24}H_{30}N_2O_3^+$; calc. 395.2335).

*4-[(*tert-*Butoxy)carbonyl]-1-[(4-chlorophenyl)methyl]-6-(phenylmethyl)piperazin-2-one* (**25**). Yield 100%, based on the amine. IR: 2976, 2928, 1697, 1654, 1491, 1472, 1457, 1419, 1405, 1366, 1323, 1270, 1242, 1165, 1131, 1088, 1064, 1016, 964, 925, 877, 849. ^{1}H-NMR ($CDCl_3$): 7.36–7.08 (*m*, 9 H); 5.35 (*d*, *J* = 15.1, 1 H); 4.52–4.30 (*m*, 1 H); 4.14–4.00 (*m*, 0.6 H); 3.97–3.73 (*m*, 2.4 H); 3.34 (*m*, 1 H); 3.00–2.76 (*m*, 2 H); 2.75 (*dd*, *J* = 13.5, 9.7, 1 H); 1.55–1.41 (*m*, 9 H). HR-MS: 415.1775 ($[M+H]^+$, $C_{23}H_{27}ClN_2O_3^+$; calc. 415.1788).

*4-[(*tert-*Butoxy)carbonyl]-6-(phenylmethyl)1-{[3-(trifluoromethyl)phenyl]methyl}piperazin-2-one* (**26**). Yield 100%, based on the amine. IR: 2976, 2928, 1692, 1654, 1452, 1414, 1390, 1366, 1328, 1242, 1160, 1122, 1093, 1074, 1021, 964, 877, 700. ^{1}H-NMR ($CDCl_3$): 7.60–7.38 (*m*, 4 H); 7.36–7.08 (*m*, 5 H); 5.42 (*d*, *J* = 15.1, 1 H); 4.53–4.30 (*m*, 1 H); 4.16–4.01 (*m*, 0.8 H); 4.00–3.81 (*m*, 2.2 H); 3.33 (*m*, 1 H); 3.01–2.80 (*m*, 2 H); 2.77 (*dd*, *J* = 13.5, 9.4, 1 H); 1.53–1.38 (br. *s*, 9 H). HR-MS: 471.1886 ($[M+Na]^+$, $C_{24}H_{27}F_3N_2O_3^+$; calc. 471.1871).

*4-[(*tert-*Butoxy)carbonyl]-1-[(furan-2-yl)methyl]-6-(phenylmethyl)piperazin-2-one* (**27**). Yield 100%, based on the amine. IR: 2975, 2929, 1700, 1653, 1558, 1540, 1506, 1472, 1457, 1419, 1369, 1324, 1272, 1247, 1166, 1128, 1078, 1009, 962, 935, 883, 743, 700, 668. ^{1}H-NMR ($CDCl_3$): 7.43–7.09 (*m*, 6 H); 6.39–6.25 (*m*, 2 H); 5.15 (*d*, *J* = 15.6, 1 H); 4.48–4.25 (*m*, 1 H); 4.19–3.98 (*m*, 1.6 H); 3.96–3.77 (*m*, 1.4 H); 3.58–3.43 (*m*, 1 H); 3.02–2.80 (*m*, 2 H); 2.70 (*dd*, *J* = 13, 10, 1 H); 1.56–1.40 (br. *s*, 9 H). HR-MS: 371.1979 ($[M+H]^+$, $C_{21}H_{26}N_2O_4^+$; calc. 371.1971).

*4-[(*tert-*Butoxy)carbonyl]-1-[(4-methoxyphenyl)methyl]-6-(2-phenylethyl)piperazin-2-one* (**28**). Yield 100%, based on the amine. IR: 2971, 2930, 1696, 1650, 1557, 1506, 1450, 1419, 1239, 1168, 1127, 1070, 1034, 701. ^{1}H-NMR ($CDCl_3$): 7.34–7.17 (*m*, 3 H); 7.15–7.08 (*m*, 2 H); 6.95 (*d*, *J* = 8.4, 2 H); 6.75 (*d*, *J* = 8.4, 2 H); 5.22 (*d*, *J* = 14.6, 1 H); 4.52–4.04 (*m*, 2 H); 3.91–3.79 (*m*, 1 H); 3.76 (*s*, 3 H); 3.64 (*d*, *J* = 14.6, 1 H); 3.20–2.72 (*m*, 3 H); 2.53–2.38 (*m*, 1 H); 1.93–1.72 (*s*, 2 H); 1.47 (*s*, 9 H). HR-MS: 425.2446 ($[M+H]^+$, $C_{25}H_{32}N_2O_4^+$; calc. 425.2440).

*4-[(*tert-*Butoxy)carbonyl]-1-[(4-methylphenyl)methyl]-6-(2-phenylethyl)piperazin-2-one* (**29**). Yield 100%, based on the amine. IR: 2923, 2862, 1692, 1646, 1451, 1415, 1241, 1164, 1128, 749, 697. ^{1}H-NMR ($CDCl_3$): 7.34–7.08 (*m*, 5 H); 7.06 (*d*, *J* = 7.6, 2 H); 6.93 (*d*, *J* = 7.6, 2 H); 5.24 (*d*, *J* = 14.6, 1 H); 4.54–4.03 (*m*, 2 H); 3.94–3.78

(*m*, 1 H); 3.69 (*d*, *J* = 14.6, 1 H); 3.21–2.67 (*m*, 3 H); 2.53–2.39 (*m*, 1 H); 2.31 (*s*, 3 H); 1.94–1.74 (*m*, 2 H); 1.48 (*s*, 9 H). HR-MS: 409.2497 ($[M+H]^+$, $C_{25}H_{32}N_2O_3^+$; calc. 409.2491).

*4-[(*tert*-Butoxy)carbonyl]-1-[(4-chlorophenyl)methyl]-6-(2-phenylethyl)piperazin-2-one* (**30**). Yield 100%, based on the amine. IR: 2973, 2930, 1693, 1649, 1417, 1363, 1239, 1163, 1126, 1088, 753, 699. ^{1}H-NMR ($CDCl_3$): 7.35–7.19 (*m*, 3 H); 7.18 (*d*, *J* = 8.4, 2 H); 7.15–7.08 (*m*, 2 H); 6.92 (*d*, *J* = 8.4, 2 H); 5.20 (*d*, *J* = 14.6, 1 H); 4.54–4.05 (*m*, 2 H); 3.94–3.76 (*m*, 1 H); 3.65 (*d*, *J* = 14.6, 1 H); 3.17–2.74 (*m*, 3 H); 2.55–2.38 (*m*, 1 H); 1.94–1.79 (*m*, 2 H); 1.47 (*s*, 9 H). HR-MS: 429.1936 ($[M+H]^+$, $C_{24}H_{29}ClN_2O_3^+$; calc. 429.1945).

*4-[(*tert*-Butoxy)carbonyl]-6-(2-phenylethyl)-1-{[(3-(trifluoromethyl)phenyl]methyl}piperazin-2-one* (**31**). Yield 100%, based on the amine. IR: 2965, 2922, 1689, 1654, 1645, 1452, 1417, 1325, 1241, 1162, 1123, 1070, 698. ^{1}H-NMR ($CDCl_3$): 7.49 (br. *d*, *J* = 7.6, 1 H); 7.36 (*t*, *J* = 7.6, 1 H); 7.33–7.15 (*m*, 5 H); 7.15–7.07 (*m*, 2 H); 5.25 (*d*, *J* = 15.1, 1 H); 4.57–4.08 (*m*, 2 H); 3.96–3.81 (*m*, 1 H); 3.78 (*d*, *J* = 15.1, 1 H); 3.18–2.66 (*m*, 3 H); 2.54–2.34 (*m*, 1 H); 1.97–1.80 (*m*, 2 H); 1.48 (*s*, 9 H). HR-MS: 485.2016 ($[M+Na]^+$, $C_{25}H_{29}F_3N_2O_3^+$; calc. 485.2028).

*4-[(*tert*-Butoxy)carbonyl]-1-[(furan-2-yl)methyl]-6-(2-phenylethyl)piperazin-2-one* (**32**). Yield 100%, based on the amine. IR: 2965, 2922, 1689, 1654, 1417, 1364, 1320, 1246, 1162, 1123, 1009, 746. ^{1}H-NMR ($CDCl_3$): 7.36–7.11 (*m*, 6 H); 6.30–6.24 (*m*, 1 H); 6.10 (*d*, *J* = 3.0, 1 H); 5.05 (*d*, *J* = 15.4, 1 H); 4.50–4.08 (*m*, 2 H); 4.02 (*d*, *J* = 15.4, 1 H); 3.91–3.74 (*m*, 1 H); 3.36–2.94 (*m*, 2 H); 2.88–2.72 (*m*, 1 H); 2.58–2.46 (*m*, 1 H); 1.94–1.71 (*m*, 2 H); 1.47 (*s*, 9 H). HR-MS: 385.2119 ($[M+H]^+$, $C_{22}H_{28}N_2O_4^+$; calc. 385.2127).

4-Benzyl-6-ethyl-1-{[3-(trifluoromethyl)phenyl]methyl}piperazin-2-one (**11**). A soln. of **10** (10.5 mg, 0.027 mmol) in 3.2M HCl/AcOEt (0.5 ml) was stirred at 25° for 1 h before solvent and excess acid were removed under a stream of N_2. The residue was dried under high vacuum for 5 h, and treated with a soln. of $EtN(i\text{-}Pr)_2$ in DMF (0.1M, 0.35 ml, 0.035 mmol) and a soln. of $PhCH_2Br$ in DMF (0.1M, 0.29 ml, 0.029 mmol) and stirred at 25° for 17 h. The mixture was extracted with AcOEt (10 ml) and washed with H_2O (2 × 5 ml) and sat. aq. NaCl soln. (5 ml), dried ($MgSO_4$), and evaporated to afford **11** (9.8 mg, 96%). ^{1}H-NMR ($CDCl_3$): 7.58–7.18 (*m*, 9 H); 5.29 (*d*, *J* = 15.4, 1 H); 4.05 (*d*, *J* = 15.4, 1 H); 3.64 (*d*, *J* = 13.0, 1 H); 3.48 (*d*, *J* = 16.5, 1 H); 3.44 (*d*, *J* = 13.0, 1 H); 3.07 (*d*, *J* = 16.5, 1 H); 3.03 (*m*, 1 H); 2.75 (br. *d*, *J* = 11.9, 1 H); 2.37 (*dd*, *J* = 11.9, 3.8, 1 H); 1.84 (*m*, 1 H); 1.63 (*m*, 1 H); 0.70 (*t*, *J* = 7.3, 3 H). IR: 2961, 2930, 1648, 1463, 1448, 1427, 1327, 1158, 1121, 1074, 916, 800, 747, 694. HR-MS: 377.1844 ($[M+H]^+$, $C_{21}H_{23}F_3N_2O^+$; calc. 377.1841).

6-Ethyl-4-(4-methoxybenzyl)-1-{[3-(trifluoromethyl)phenyl]methyl}piperazin-2-one (**12**). A soln. of **10** (7.5 mg, 0.020 mmol) in 3.2M HCl/AcOEt (0.5 ml) was stirred at 25° for 1 h before the solvent and excess acid were removed under a stream of N_2. The resulting residue was dissolved in 1,2-dichloroethane (2.0 ml) and treated with a soln. of 4-methoxybenzaldehyde in 1,2-dichloroethane (0.1M, 0.23 ml, 0.023 mmol), AcOH (2.3 µl, 0.040 mmol), and $NaBH(OAc)_3$ (11 mg, 0.053 mmol), and stirred at 25° for 40 h. The mixture was extracted with AcOEt (10 ml) and washed with sat. aq. $NaHCO_3$ (3 × 5 ml) and sat. aq. NaCl soln. (5 ml), dried ($MgSO_4$), and concentrated to afford **12** (8.0 mg, 100%). ^{1}H-NMR ($CDCl_3$): 7.57–7.37 (*m*, 4 H); 7.20 (*d*, *J* = 8.4, 2 H); 6.84 (*d*, *J* = 8.4, 2 H); 5.27 (*d*, *J* = 15.4, 1 H); 4.04 (*d*, *J* = 15.4, 1 H); 3.78 (*s*, 3 H); 3.55 (*d*, *J* = 12.7, 1 H); 3.44 (*d*, *J* = 16.5, 1 H); 3.35 (*d*, *J* = 12.7, 1 H); 3.06 (*d*, *J* = 16.5, 1 H); 2.99 (*m*, 1 H); 2.72 (br. *d*, *J* = 11.6, 1 H); 2.33 (*dd*, *J* = 11.6, 3.8, 1 H); 1.80 (*m*, 1 H); 1.60 (*m*, 1 H); 0.69 (*t*, *J* = 7.3, 3 H). IR: 2919, 1649, 1508, 1461, 1326, 1243, 1161, 1114, 1007, 1032, 814, 703. HR-MS: 407.1942 ($[M+H]^+$, $C_{22}H_{25}F_3N_2O_2^+$; calc. 407.1946).

*2-([(*tert*-Butoxy)carbonyl]{2-[(4-methoxybenzyl)amino]-2-oxoethyl}amino)acetic Acid* (**13**). A soln. of *N*-Boc-iminodiacetic acid (**1**, 500 mg, 2.15 mmol) in DMF (6.5 ml) was treated with EDCI (433 mg, 2.25 mmol) and stirred at 25° for 1 h. 4-Methoxybenzylamine (300 mg, 2.15 mmol) was added, and the mixture stirred for an additional 20 h, and then poured into a separatory funnel containing 10% aq. HCl (50 ml) and extracted with AcOEt (100 ml). The org. phase was washed with 10% aq. HCl (2 × 50 ml) and sat. aq. NaCl soln. (50 ml), dried ($MgSO_4$), and concentrated to afford **13** (704 mg, 93%). Amorphous solid: ^{1}H-NMR ($CDCl_3$): 7.41 (br. *s*, 1 H); 7.23–7.14 (*m*, 2 H); 6.91–6.78 (*m*, 2 H); 6.54 (*m*, 1 H); 4.46–4.35 (*m*, 2 H); 4.03–3.91 (*m*, 3 H); 3.88 (br. *s*, 1 H); 3.78, 3.78 (*s*, 2 H); 3.77 (*s*, 1 H); 1.43 (*s*, 6 H); 1.33 (*s*, 3 H).

*4-[(*tert*-Butoxy)carbonyl]-1-[(4-methoxyphenyl)methyl]piperazine-2,6-dione* (**14**). A soln. of **13** (253 mg, 0.73 mmol) in THF (5.0 ml) was treated with 1,1′-carbonyldiimidazole (CDI; 472 mg, 2.90 mmol) and stirred at 25° for 18 h. The solvent was removed *in vacuo*, and the residue was dissolved in AcOEt (30 ml) and washed sequentially with 10% aq. HCl (2 × 10 ml), sat. aq. NaCl (10 ml), sat. aq. $NaHCO_3$ (2 × 10 ml), and sat. aq. NaCl (10 ml) solns. The org. phase was dried ($MgSO_4$) and concentrated to afford **14** (214 mg, 90%). ^{1}H-NMR ($CDCl_3$): 7.34 (*d*, *J* = 8.8, 2 H); 6.81 (*d*, *J* = 8.8, 2 H); 4.87 (*s*, 2 H); 4.30 (*s*, 4 H); 3.76 (*s*, 3 H); 1.44 (*s*, 9 H). HR-MS: 357.1438 ($[M+Na]^+$, $C_{17}H_{22}N_2O_5^+$; calc. 357.1426).

*2-[[(*tert*-Butoxy)carbonyl][2-(4-methylphenyl)-2-oxoethyl]amino]-*N*-(4-methoxybenzyl)acetamide* (**15**). A soln. of **14** (161 mg, 0.48 mmol) in THF (3.2 ml) was cooled to 0° and treated with 4-toluoylmagnesium

bromide (1.0M in Et_2O, 0.72 ml, 0.72 mmol). The mixture was stirred for 2 h, warmed to 25° for 1 h, and then cooled back to 0° and quenched by addition of sat. aq. NH_4Cl (3 ml) soln. The mixture was extracted with AcOEt (30 ml) and washed with H_2O (2 × 10 ml) and sat. aq. NaCl soln. (10 ml). The org. phase was dried ($MgSO_4$), concentrated under reduced pressure, and FC (SiO_2; 0–2% MeOH/$CHCl_3$) afforded **15** (44 mg, 21%). Colorless oil: ^{1}H-NMR ($CDCl_3$): 8.71 (*m*, 1 H); 8.18 (*m*, 1 H); 7.80 (*d*, *J* = 8.4, 2 H); 7.75 (*d*, *J* = 8.1, 1 H); 7.38–7.15 (*m*, 2 H); 6.84 (*d*, *J* = 8.4, 2 H); 6.79 (*d*, *J* = 8.1, 1 H); 4.68 (br. *s*, 2 H); 4.59 (br. *s*, 1 H); 4.48–4.37 (*m*, 2 H); 4.01 (br. *s*, 1 H); 3.90 (br. *s*, 1 H); 3.77 (*s*, 2 H); 3.75 (*s*, 1 H); 2.41 (*s*, 1 H); 2.40 (*s*, 2 H); 1.39 (*s*, 6 H); 1.29 (*s*, 3 H). HR-MS: 427.2219 ($[M+H]^+$, $C_{24}H_{30}N_2O_5^+$; calc. 427.2233).

*2-[[(*tert*-Butoxy)carbonyl][2-hydroxy-2-(4-methylphenyl)ethyl]amino]-*N*-(4-methoxybenzyl)acetamide* (**17**). A soln. of **15** (41.7 mg, 0.098 mmol) in MeOH/THF 1:1 (1 ml) was cooled to 0°, treated with $NaBH_4$ (4.0 mg, 0.10 mmol), warmed to 25°, and stirred for 1.5 h. The mixture was diluted with sat. aq. $NaHCO_3$ soln. (10 ml) and extracted with AcOEt (25 ml). The org. phase was washed with H_2O (25 ml) and sat. aq. NaCl soln. (25 ml), dried ($MgSO_4$), and concentrated. FC (SiO_2; 50% AcOEt/hexanes) provided **17** (25 mg, 60%). Viscous oil: ^{1}H-NMR ($CDCl_3$): 7.32–7.18 (*m*, 2 H); 7.20 (*d*, *J* = 8.4, 2 H); 7.14 (*d*, *J* = 8.1, 2 H); 6.88 (*d*, *J* = 8.4, 2 H); 6.77 (br. *s*, 0.5 H); 6.36 (br. *s*, 0.5 H); 5.00–4.89 (*m*, 1 H); 4.50–4.28 (*m*, 2 H); 4.10–3.95 (*m*, 1 H); 3.92–3.60 (*m*, 2 H); 3.77 (*s*, 3 H); 3.56–3.27 (*m*, 1 H); 3.19–3.04 (*m*, 0.5 H); 2.32 (*s*, 3 H); 1.47 (br. *s*, 4.5 H); 1.36 (br. *s*, 4.5 H). HR-MS: 429.2379 ($[M+H]^+$, $C_{24}H_{32}N_2O_5^+$; calc. 427.2389).

General Procedure for the Final Coupling Reaction: 6-Ethyl-4-(4-methoxybenzoyl)-1-[(4-methoxyphenyl)-methyl]piperazin-2-one (**33**, **A1B1C1**). A portion of **8** (80.3 mg, 0.276 mmol) was treated with 3.2M HCl/AcOEt (1 ml) and stirred at 25° for 1 h before the solvent and excess acid were removed under a stream of N_2, followed by high vacuum for 4 h. The resulting residue was dissolved in DMF (1 ml) and treated with 4-methoxybenzoic acid (41.9 mg, 0.276 mmol), $EtN(i\text{-}Pr)_2$ (53 µl, 0.30 mmol), and EDCI (53 mg, 0.276 mmol), and stirred at 25° for 16 h. The mixture was extracted with AcOEt (30 ml) and washed with 10% aq. HCl (3 × 10 ml), sat. aq. $NaHCO_3$ (3 × 10 ml), and sat. aq. NaCl (10 ml) solns. Drying ($MgSO_4$) and evaporation afforded **33**, **A1B1C1** (80 mg,76%). Colorless viscous oil. IR: 2963, 2926, 1639, 1606, 1507, 1423, 1241, 1170, 1030, 842. ^{1}H-NMR ($CDCl_3$): 7.35 (*d*, *J* = 8.6, 2 H); 7.16 (*d*, *J* = 8.6, 2 H); 6.90 (*d*, *J* = 8.6, 2 H); 6.84 (*d*, *J* = 8.6, 2 H); 5.32 (*d*, *J* = 14.6, 1 H); 4.91–4.00 (*m*, 3 H); 3.82 (*s*, 3 H); 3.80 (*d*, *J* = 14.6, 1 H); 3.32–2.96 (*m*, 2 H); 1.77–1.38 (*m*, 2 H); 1.14–0.45 (*m*, 3 H). HR-MS: 383.1974 ($[M+H]^+$, $C_{22}H_{26}N_2O_4^+$; calc. 383.1971).

4-(4-Bromobenzoyl)-6-ethyl-1-[(4-methoxyphenyl)methyl]piperazin-2-one (**9**). Yield 89%. ^{1}H-NMR ($CDCl_3$): 7.83 (*d*, *J* = 7.8, 1 H); 7.81 (*d*, *J* = 7.3, 1 H); 7.26 (*d*, *J* = 7.8, 1 H); 7.23 (*d*, *J* = 7.3, 1 H); 4.81 (*s*, 1 H); 4.69 (*s*, 1 H); 4.15 (*s*, 1 H); 4.04 (*s*, 1 H); 3.713 (*s*, 1.5 H); 3.708 (*s*, 1.5 H); 2.40 (*s*, 1.5 H); 2.39 (*s*, 1.5 H); 1.43 (*s*, 4.5 H); 1.36 (*s*, 4.5 H). HR-MS: 431.0979 ($[M+H]^+$, $C_{21}H_{23}BrN_2O_3^+$; calc. 431.0970).

6-Ethyl-4-(4-methylbenzoyl)-1-[(4-methylphenyl)methyl]piperazin-2-one (**33**, **A1B2C2**). IR: 2954, 2923, 1646, 1631, 1415, 1256, 831. ^{1}H-NMR ($CDCl_3$): 7.35–7.05 (*m*, 8 H); 5.35 (*d*, *J* = 14.6, 1 H); 5.03–4.15 (*m*, 2 H); 4.07 (*d*, *J* = 18.4, 1 H); 3.81 (*d*, *J* = 14.6, 1 H); 3.45–2.84 (*m*, 2 H); 2.36 (*s*, 3 H); 2.32 (*s*, 3 H); 1.85–1.35 (*m*, 2 H); 1.16–0.39 (*m*, 3 H). HR-MS: 351.2076 ($[M+H]^+$, $C_{22}H_{26}N_2O_2^+$; calc. 351.2073).

4-(4-Chlorobenzoyl)-1-[(4-chlorophenyl)methyl]-6-ethylpiperazin-2-one (**33**, **A1B3C3**). IR: 2971, 2930, 1645, 1424, 1255, 1157, 1091, 1014. ^{1}H-NMR ($CDCl_3$): 7.40 (*d*, *J* = 8.4, 2 H); 7.33 (*d*, *J* = 8.4, 2 H); 7.28 (*d*, *J* = 8.4, 2 H); 7.17 (*d*, *J* = 8.4, 2 H); 5.28 (*d*, *J* = 14.8, 1 H); 5.03–4.01 (*m*, 3 H); 3.88 (*d*, *J* = 14.8, 1 H); 3.84–2.79 (*m*, 2 H); 1.87–1.37 (*m*, 2 H); 1.22–0.44 (*m*, 3 H). HR-MS: 391.0982 ($[M+H]^+$, $C_{20}H_{20}Cl_2N_2O_2^+$; calc. 391.0980).

*6-Ethyl-4-[(1*H*-pyrrol-2-yl)carbonyl]-1-{[(3-(trifluoromethyl)phenyl]methyl}piperazin-2-one* (**33**, **A1B4C4**). IR: 3271, 2967, 2938, 1657, 1643, 1605, 1429, 1325, 1163, 1120, 1068. ^{1}H-NMR ($CDCl_3$): 9.56 (br. *s*, 1 H); 7.62–7.35 (*m*, 4 H); 6.96 (br. *s*, 1 H); 6.66 (br. *s*, 1 H); 6.29 (*m*, 1 H); 5.35 (*d*, *J* = 15.1, 1 H); 4.81 (*d*, *J* = 17.6, 1 H); 4.75–4.55 (*m*, 1 H); 4.48–4.29 (*m*, 1 H); 4.05 (*d*, *J* = 15.1, 1 H); 3.28–3.09 (*m*, 2 H); 1.79–1.43 (*m*, 2 H); 0.94 (*t*, *J* = 7.0, 3 H). HR-MS: 380.1589 ($[M+H]^+$, $C_{19}H_{20}F_3N_3O_2^+$; calc. 380.1586).

6-Ethyl-4-[(furan-2-yl)carbonyl]-1-[(furan-2-yl)methyl]piperazin-2-one (**33**, **A1B5C5**). IR: 2965, 2930, 1658, 1641, 1483, 1426, 1277, 1189, 1013, 755. ^{1}H-NMR ($CDCl_3$): 7.50 (br. *s*, 1 H); 7.35 (*d*, *J* = 1.1, 1 H); 7.11 (*d*, *J* = 3.5, 1 H); 6.50 (*dd*, *J* = 3.5, 1.9, 1 H); 6.32 (*dd*, *J* = 3.0, 1.9, 1 H); 6.29 (*d*, *J* = 3.2, 1 H); 5.15 (*d*, *J* = 15.4, 1 H); 4.93–4.70 (*m*, 1 H); 4.66 (br. *d*, *J* = 13.2, 1 H); 4.47–4.15 (*m*, 1 H); 4.10 (*d*, *J* = 15.4, 1 H); 3.61–2.95 (*m*, 2 H); 1.81–1.42 (*m*, 2 H); 1.12–0.71 (*m*, 3 H). HR-MS: 303.1339 ($[M+H]^+$, $C_{16}H_{18}N_2O_4^+$; calc. 303.1345).

6-Ethyl-1-[(4-methoxyphenyl)methyl]-4-[(thiophen-2-yl)carbonyl]piperazin-2-one (**33**, **A1B1C6**). IR: 2965, 2950, 1649, 1619, 1513, 1426, 1241, 1176, 1031, 991, 847, 820, 733. ^{1}H-NMR ($CDCl_3$): 7.48 (*dd*, *J* = 5.0, 0.8, 1 H); 7.35 (br. *d*, *J* = 3.5, 1 H); 7.17 (*d*, *J* = 8.6, 2 H); 7.05 (*dd*, *J* = 5.0, 3.5, 1 H); 6.85 (*d*, *J* = 8.6, 2 H); 5.32 (*d*, *J* = 14.6, 1 H); 4.70 (*d*, *J* = 18.1, 1 H); 4.60–4.38 (*m*, 1 H); 4.36–4.15 (*m*, 1 H); 3.83 (*d*, *J* = 14.6, 1 H); 3.78

(*s*, 3 H); 3.29–3.06 (*m*, 2 H); 1.76–1.44 (*m*, 2 H); 0.98–0.76 (*m*, 3 H). HR-MS: 359.1425 ([$M+H$]$^+$, $C_{19}H_{22}N_2OS^+$; calc. 359.1429).

*6-Ethyl-4-[(1*H*-indol-2-yl)carbonyl]-1-[(4-methylphenyl)methyl]piperazin-2-one* (**33**, **A1B2C7**). IR: 3281, 2962, 2926, 1638, 1608, 1428, 1411, 1345, 1244, 1161, 1139, 1073, 981, 911, 805. ^{1}H-NMR ($CDCl_3$): 9.28 (br. *s*, 1 H); 7.66 (br. *d*, *J* = 7.8, 1 H); 7.41 (*d*, *J* = 8.4, 1 H); 7.19–7.05 (*m*, 5 H); 6.91 (br. *s*, 1 H); 5.38 (*d*, *J* = 14.6, 1 H); 5.00–4.80 (*m*, 1 H); 4.79–4.61 (*m*, 1 H); 4.60–4.25 (*m*, 1 H); 3.88 (*d*, *J* = 14.6, 1 H); 3.31–3.12 (*m*, 2 H); 2.34 (*s*, 3 H); 1.79–1.41 (*m*, 2 H); 1.08–0.75 (*m*, 3 H). HR-MS: 376.2029 ([$M+H$]$^+$, $C_{23}H_{25}N_3O_2^+$; calc. 376.2025).

4-[([1]Benzofuran-2-yl)carbonyl]-1-[(4-chlorophenyl)methyl]-6-ethylpiperazin-2-one (**33**, **A1B3C8**). IR: 2962, 2927, 2874, 2656, 2634, 1424, 1411, 1292, 1253, 1231, 1173, 1090, 1011, 914, 800, 739. ^{1}H-NMR ($CDCl_3$): 7.66 (*d*, *J* = 7.8, 1 H); 7.51 (br. *s*, 1 H); 7.45 (*s*, 1 H); 7.42 (*t*, *J* = 7.6, 1 H); 7.34–7.15 (*m*, 5 H); 5.31 (br. *d*, *J* = 14.6, 1 H); 5.13–4.78 (*d*, *J* = 13.0, 1 H); 4.64–4.31 (*m*, 1 H); 3.95 (*d*, *J* = 14.6, 1 H); 3.62–2.96 (*m*, 2 H); 1.81–1.49 (*m*, 2 H); 1.08–0.79 (*m*, 3 H). HR-MS: 397.1316 ([$M+H$]$^+$, $C_{22}H_{21}ClN_2O_3^+$; calc. 397.1319).

4-[([1]Benzothiophen-2-yl)carbonyl]-6-ethyl-1-{[3-(trifluoromethyl)phenyl]methyl}piperazine (**33**, **A1B4C9**). IR: 2969, 2933, 1655, 1638, 1410, 1322, 1283, 1243, 1164, 1120, 1063, 993, 752, 704. ^{1}H-NMR ($CDCl_3$): 7.89–7.72 (*m*, 2 H); 7.61–7.30 (*m*, 7 H); 5.37 (*d*, *J* = 15.1, 1 H); 4.79 (*d*, *J* = 18.1, 1 H); 4.69–4.19 (*m*, 2 H); 4.03 (*d*, *J* = 15.1, 1 H); 3.47–3.04 (*m*, 2 H); 1.81–1.45 (*m*, 2 H); 1.05–0.67 (*m*, 3 H). HR-MS: 447.1341 ([$M+H$]$^+$, $C_{23}H_{21}F_3N_2O_2S^+$; calc. 447.1354).

6-Ethyl-1-[(furan-2-yl)methyl]-4-(3-phenylprop-2-enoyl)piperazin-2-one (**33**, **A1B5C10**). IR: 2969, 2933, 2872, 1649, 1610, 1427, 1357, 1331, 1278, 1225, 1199, 1155, 1068, 1006, 980, 765. ^{1}H-NMR ($CDCl_3$): 7.72 (*d*, *J* = 15.1, 1 H); 7.51 (br. *s*, 1 H); 7.43–7.28 (*m*, 4 H); 6.78 (*d*, *J* = 15.1, 1 H); 6.36–6.32 (*m*, 1 H); 6.30 (*d*, *J* = 3.2, 1 H); 5.14 (*d*, *J* = 15.1, 1 H); 4.72 (*d*, *J* = 13.0, 1 H); 4.49 (*d*, *J* = 17.6, 0.7 H); 4.21 (*d*, *J* = 17.6, 1 H); 4.11 (*d*, *J* = 15.1, 1 H); 3.97 (*d*, *J* = 17.6, 0.3 H); 3.52–3.40 (*m*, 0.3 H); 3.34 (*m*, 1 H); 3.04 (br. *d*, *J* = 13.2, 0.7 H); 1.78–1.35 (*m*, 2 H); 0.98 (br. *t*, *J* = 7.3, 3 H). HR-MS: 339.1706 ([$M+H$]$^+$, $C_{20}H_{22}N_2O_3^+$; calc. 339.1709).

6-Benzyl-4-(4-methoxybenzoyl)-[(4-methoxyphenyl)methyl]piperazin-2-one (**33**, **A2B1C1**). IR: 2925, 1655, 1607, 1423, 1296, 1243, 1173, 1023, 958, 844, 756, 699. ^{1}H-NMR ($CDCl_3$): 7.40 (*d*, *J* = 8.6, 2 H); 7.35–7.10 (*m*, 5 H); 7.16 (*d*, *J* = 8.6, 2 H); 6.96–6.80 (*m*, 2 H); 6.85 (*d*, *J* = 8.6, 2 H); 5.36 (*d*, *J* = 14.9, 1 H); 4.68–4.16 (*m*, 1 H); 4.09 (*d*, *J* = 18.3, 1 H); 3.85 (*m*, 1 H); 3.82 (*s*, 3 H); 3.78 (*s*, 3 H); 3.71 (*m*, 1 H); 3.49–3.37 (*m*, 1 H); 3.25–2.55 (*m*, 3 H). HR-MS: 445.2114 ([$M+H$]$^+$, $C_{27}H_{28}N_2O_4^+$; calc. 445.2127).

6-Benzyl-4-(4-methylbenzoyl)-1-[(4-methylphenyl)methyl]piperazin-2-one (**33**, **A2B2C2**). IR: 2916, 1655, 1638, 1427, 1414, 1252, 1212, 1182, 1155, 1076, 1024, 826, 747, 704. ^{1}H-NMR ($CDCl_3$): 7.45–6.90 (*m*, 13 H); 5.39 (*d*, *J* = 14.6, 1 H); 5.01–3.93 (*m*, 3 H); 3.90–3.11 (*m*, 2 H); 3.10–2.50 (*m*, 2 H); 2.36 (*s*, (3 H); 2.31 (*s*, 3 H). HR-MS: 413.2217 ([$M+H$]$^+$, $C_{27}H_{28}N_2O_2^+$; calc. 413.2229).

6-Benzyl-4-(4-chlorobenzoyl)-1-[(4-chlorophenyl)methyl]piperazin-2-one (**33**, **A2B3C3**). IR: 2927, 1655, 1638, 1427, 1410, 1256, 1155, 1090, 1011, 840, 730. ^{1}H-NMR ($CDCl_3$): 7.51–6.98 (*m*, 13 H); 5.35 (*d*, *J* = 15.1, 1 H); 4.99–3.95 (*m*, 3 H); 3.98–3.15 (*m*, 2 H); 3.12–2.44 (*m*, 3 H). HR-MS: 453.1127 ([$M+H$]$^+$, $C_{25}H_{22}Cl_2N_2O_2^+$; calc. 453.1137).

*6-Benzyl-4-[(1*H*-pyrrol-2-yl)carbonyl]-1-{[3-(trifluoromethyl)phenyl]methyl}piperazin-2-one* (**33**, **A2B4C4**). IR: 3275, 2915, 1655, 1642, 1427, 1326, 1164, 1124, 1072, 966. ^{1}H-NMR ($CDCl_3$): 9.53 (br. *s*, 0.4 H); 7.61–6.94 (*m*, 11.4 H); 6.58 (br. *s*, 0.6 H); 6.28 (br. *s*, 0.6 H); 5.44 (*d*, *J* = 15.1, 0.4 H); 5.39 (*d*, *J* = 15.1, 0.6 H); 4.84 (*d*, *J* = 18.1, 0.6 H); 4.70–4.29 (*m*, 2.4 H); 4.03 (*d*, *J* = 15.1, 0.4 H); 3.81 (*d*, *J* = 15.1, 0.6 H); 3.46 (*m*, 0.6 H); 3.32 (*m*, 0.4 H); 3.20–2.68 (*m*, 3 H). HR-MS: 442.1728 ([$M+H$]$^+$, $C_{24}H_{22}F_3N_3O_2^+$; calc. 442.1742).

6-Benzyl-3-[(furan-2-yl)carbonyl]-1-[(furan-2-yl)methyl]piperazin-2-one (**33**, **A2B5C5**). IR: 3117, 2924, 1659, 1642, 1480, 1427, 1352, 1326, 1273, 1225, 1190, 1146, 1059, 1010, 888. ^{1}H-NMR ($CDCl_3$): 7.59–6.83 (*m*, 8 H); 6.49 (br. *s*, 1 H); 6.38–6.26 (*m*, 2 H); 5.17 (*d*, *J* = 15.4, 1 H); 4.87 (br. *d*, *J* = 18.4, 1 H); 4.70–4.00 (*m*, 2 H); 4.06 (*d*, *J* = 15.4, 1 H); 3.63 (*m*, 1 H); 3.28–2.53 (*m*, 3 H). HR-MS: 365.1508 ([$M+H$]$^+$, $C_{21}H_{20}N_2O_4^+$; calc. 365.1501).

6-Benzyl-1-[(4-methoxyphenyl)methyl][(thiophen-2-yl)carbonyl]piperazin-2-one (**33**, **A2B1C6**). IR: 2933, 1651, 1611, 1510, 1428, 1361, 1248, 1171, 1028, 910, 853, 735. ^{1}H-NMR ($CDCl_3$): 7.49 (*d*, *J* = 4.3, 1 H); 7.37–6.94 (*m*, 9 H); 6.85 (*d*, *J* = 8.6, 2 H); 5.35 (*d*, *J* = 14.8, 1 H); 4.74 (br. *d*, *J* = 18.4, 1 H); 4.56–4.31 (*m*, 1 H); 4.24 (br. *d*, *J* = 18.4, 1 H); 3.79 (*s*, 3 H); 3.75 (*d*, *J* = 14.8, 1 H); 3.47 (*m*, 1 H); 3.21–3.03 (*m*, 1 H); 2.90 (*dd*, *J* = 13.5, 4.3, 1 H); 2.72 (*m*, 1 H). HR-MS: 421.1594 ([$M+H$]$^+$, $C_{24}H_{24}N_2O_3S^+$; calc. 421.1586).

*6-Benzyl-4-[(1*H*-indol-2-yl)carbonyl]-1-[(4-methylphenyl)methyl]piperazin-2-one* (**33**, **A2B2C7**). IR: 3278, 3014, 2921, 1650, 1614, 1516, 1424, 1336, 1316, 1244, 1127, 1085, 808, 747, 705. ^{1}H-NMR ($CDCl_3$): 9.34 (br. *s*, 1 H); 7.63 (br. *s*, 1 H); 7.43 (*d*, *J* = 8.4, 1 H); 7.31 (*t*, *J* = 8.4, 1 H); 7.29–7.00 (*m*, 11 H); 5.41 (*d*, *J* = 14.6, 1 H); 4.90 (br. *d*, *J* = 17.8, 1 H); 4.74–4.17 (*m*, 2 H); 3.78 (*d*, *J* = 14.6, 1 H); 3.38–2.98 (br. *s*, 1 H); 2.92 (*dd*, *J* = 13.5, 4.0, 1 H); 2.84–2.63 (*m*, 1 H); 2.33 (*s*, 3 H). HR-MS: 438.2188 ([$M+H$]$^+$, $C_{28}H_{27}N_3O_2^+$; calc. 438.2182).

4-[([1]Benzofuran-2-yl)carbonyl]-6-benzyl-1-[(4-chlorophenyl)methyl]piperazin-2-one (**33**, **A2B3C8**). IR: 3024, 2921, 1649, 1559, 1490, 1474, 1428, 1255, 1175, 1255, 1175, 1090, 1015, 963, 912, 803, 742, 701. ^{1}H-NMR ($CDCl_3$): 7.66 (*d*, *J* = 7.6, 1 H); 7.61 – 6.70 (*m*, 14 H); 5.38 (*d*, *J* = 14.8, 1 H); 5.17 – 4.80 (*m*, 1 H); 4.75 – 4.05 (*m*, 2 H); 3.90 – 3.69 (*m*, 1 H); 3.59 – 3.30 (*m*, 1 H); 3.15 – 2.59 (*m*, 3 H). HR-MS: 459.1480 ($[M+H]^+$, $C_{27}H_{23}ClN_2O_3^+$; calc. 459.1475).

4-[([1]Benzothiophen-2-yl)carbonyl]-6-benzyl-1-{[3-(trifluoromethyl)phenyl]methyl}piperazin-2-one (**33**, **A2B4C9**). IR: 3066, 2921, 1650, 1624, 1522, 1419, 1326, 1244, 1198, 1162, 1121, 1075, 752, 695. ^{1}H-NMR ($CDCl_3$): 7.86 (*d*, *J* = 7.6, 1 H); 7.77 (*d*, *J* = 6.7, 1 H); 7.60 – 6.93 (*m*, 12 H); 5.43 (*d*, *J* = 15.0, 1 H); 4.84 (br. *d*, *J* = 18.4, 1 H); 4.65 – 4.38 (*m*, 1 H); 4.33 (br. *d*, *J* = 18.4, 1 H); 3.83 (*d*, *J* = 15.0, 1 H); 3.48 (*m*, 1 H); 3.36 – 3.15 (*m*, 1 H); 3.07 – 2.69 (*m*, 2 H). HR-MS: 641.0498 ($[M+Cs]^+$, $C_{28}H_{23}F_3N_2O_2S^+$; calc. 641.0487).

6-Benzyl-1-[(furan-2-yl)methyl]-4-(3-phenylprop-2-enoyl)piperazin-2-one (**33**, **A2B5C10**). IR: 3024, 2932, 1650, 1609, 1496, 1450, 1424, 1337, 1224, 1157, 1085, 1070, 1008, 972, 762, 736, 695. ^{1}H-NMR ($CDCl_3$): 7.76 (*d*, *J* = 15.1, 1 H); 7.52 (br. *s*, 1 H); 7.44 – 7.00 (*m*, 10 H); 6.77 (*d*, *J* = 15.1, 0.5 H); 6.49 (*d*, *J* = 15.1, 0.5 H); 6.41 – 6.26 (*m*, 2 H); 5.18 (*d*, *J* = 15.4, 1 H); 4.85 (br. *d*, *J* = 18.4, 0.5 H); 4.68 (br. *d*, *J* = 13.5, 0.5 H); 4.46 (br. *d*, *J* = 17.6, 0.5 H); 4.29 – 3.80 (*m*, 2.5 H); 3.78 – 3.50 (*m*, 1 H); 3.42 – 3.20 (*m*, 0.5 H); 3.11 – 2.58 (*m*, 2.5 H). HR-MS: 401.1854 ($[M+H]^+$, $C_{25}H_{24}N_2O_3^+$; calc. 401.1865).

4-(4-Methoxybenzoyl)-[(4-methoxyphenyl)methyl]-6-(2-phenylethyl)piperazin-2-one (**33**, **A3B1C1**). IR: 2932, 1640, 1609, 1511, 1455, 1419, 1301, 1244, 1172, 1116, 1070, 1029, 993, 844, 762, 700. ^{1}H-NMR ($CDCl_3$): 7.40 (*d*, *J* = 8.6, 2 H); 7.34 – 7.00 (*m*, 5 H); 6.95 (*d*, *J* = 8.6, 2 H); 6.92 (*d*, *J* = 8.6, 2 H); 6.76 (*d*, *J* = 8.6, 2 H); 5.24 (*d*, *J* = 14.6, 1 H); 5.02 – 4.19 (*m*, 2 H); 4.16 – 1.01 (*m*, 1 H); 3.83 (*s*, 3 H); 3.78 (*s*, 3 H); 3.64 (*d*, *J* = 14.6, 1 H); 3.33 – 2.28 (*m*, 4 H); 1.98 – 1.71 (*m*, 2 H). HR-MS: 459.2276 ($[M+H]^+$, $C_{28}H_{30}N_2O_4^+$; calc. 459.2284).

4-(4-Methylbenzoyl)-1-[(4-methylphenyl)methyl]-6-(2-phenylethyl)piperazin-2-one (**33**, **A3B2C2**). IR: 3024, 2921, 2870, 1642, 1422, 1256, 1073, 830, 750, 701. ^{1}H-NMR ($CDCl_3$): 7.39 – 7.02 (*m*, 9 H); 7.05 (*d*, *J* = 7.8, 2 H); 6.91 (*d*, *J* = 7.8, 2 H); 5.25 (*d*, *J* = 14.6, 1 H); 4.55 – 3.98 (*m*, 3 H); 3.66 (*d*, *J* = 14.6, 1 H); 3.33 – 2.44 (*m*, 2 H); 2.41 – 2.28 (*m*, 2 H); 2.37 (*s*, 3 H); 2.30 (*s*, 3 H); 1.97 – 1.74 (*m*, 2 H). HR-MS: 427.2377 ($[M+H]^+$, $C_{28}H_{30}N_2O_2^+$; calc. 427.2386).

4-(4-Chlorobenzoyl)-1-[(4-chlorophenyl)methyl]-6-(2-phenylethyl)piperazin-2-one (**33**, **A3B3C3**). IR: 2929, 1644, 1595, 1491, 1426, 1255, 1155, 1090, 1015, 840, 753, 701. ^{1}H-NMR ($CDCl_3$): 7.40 (*d*, *J* = 8.4, 2 H); 7.38 – 7.02 (*m*, 5 H); 7.35 (*d*, *J* = 8.4, 2 H); 7.19 (*d*, *J* = 8.4, 2 H); 6.91 (*d*, *J* = 8.4, 2 H); 5.20 (*d*, *J* = 14.6, 1 H); 4.96 – 4.63 (*m*, 1 H); 4.41 – 3.98 (*m*, 1 H); 4.06 (br. *d*, *J* = 18.4, 1 H); 3.64 (*d*, *J* = 14.6, 1 H); 3.39 – 2.21 (*m*, 4 H); 1.97 – 1.71 (*m*, 2 H). HR-MS: 467.1296 ($[M+H]^+$, $C_{26}H_{24}Cl_2N_2O_2^+$; calc. 467.1293).

*6-(2-Phenylethyl)-4-[(1*H*-pyrrol-2-yl)carbonyl]-1-{[3-(trifluoromethyl)phenyl]methyl}piperazin-2-one* (**33**, **A3B4C4**). IR: 3270, 2932, 1650, 1604, 1450, 1429, 1321, 1162, 1121, 1075, 747, 700. ^{1}H-NMR ($CDCl_3$): 9.54 (br. *s*, 1 H); 7.52 (*d*, *J* = 7.6, 1 H); 7.47 – 7.07 (*m*, 6 H); 7.39 (*t*, *J* = 7.6, 1 H); 7.11 (*d*, *J* = 7.0, 1 H); 6.99 (br. *s*, 1 H); 6.67 (br. *s*, 1 H); 6.32 (*m*, 1 H); 5.25 (*d*, *J* = 14.8, 1 H); 4.86 (*d*, *J* = 17.8, 1 H); 4.81 (br. *d*, *J* = 17.8, 1 H); 3.82 (*d*, *J* = 14.8, 1 H); 3.28 – 3.01 (*m*, 2 H); 2.94 – 2.43 (*m*, 2 H); 1.97 – 1.81 (*m*, 2 H). HR-MS: 456.1910 ($[M+H]^+$, $C_{25}H_{24}F_3N_3O_2^+$; calc. 456.1899).

4-[(Furan-2-yl)carbonyl]-1-[(furan-2-yl)methyl]-6-(2-phenylethyl)piperazin-2-one (**33**, **A3B5C5**). IR: 2921, 1650, 1624, 1473, 1422, 1273, 1186, 1063, 1006, 755. ^{1}H-NMR ($CDCl_3$): 7.52 (br. *s*, 1 H); 7.36 – 6.95 (*m*, 7 H); 6.52 (*dd*, *J* = 3.5, 1.9, 1 H); 6.27 (*dd*, *J* = 3.2, 1.9, 1 H); 6.09 (*d*, *J* = 3.2, 1 H); 5.07 (*d*, *J* = 15.4, 1 H); 4.94 – 4.64 (*m*, 2 H); 4.45 – 4.16 (*m*, 1 H); 4.03 (*d*, *J* = 15.4, 1 H); 3.42 – 2.36 (*m*, 4 H); 1.95 – 1.75 (*m*, 2 H). HR-MS: 379.1664 ($[M+H]^+$, $C_{22}H_{22}N_2O_4^+$; calc. 379.1658).

1-[(4-Methoxyphenyl)methyl]-6-(2-phenylethyl)-4-[(thiophen-2-yl)carbonyl]piperazin-2-one (**33**, **A3B1C6**). IR: 2927, 1648, 1617, 1514, 1453, 1427, 1355, 1288, 1242, 1176, 1032, 980, 842, 739, 703. ^{1}H-NMR ($CDCl_3$): 7.51 (br. *d*, *J* = 5.2, 1 H); 7.38 (br. *d*, *J* = 3.2, 1 H); 7.34 – 7.02 (*m*, 5 H); 7.09 (*dd*, *J* = 4.9, 3.8, 1 H); 6.94 (*d*, *J* = 8.6, 2 H); 6.77 (*d*, *J* = 8.6, 2 H); 5.23 (*d*, *J* = 14.6, 1 H); 4.82 – 4.52 (*m*, 1 H); 4.73 (br. *d*, *J* = 17.8, 1 H); 4.37 – 4.17 (*m*, 1 H); 3.78 (*s*, 3 H); 3.66 (*d*, *J* = 14.6, 1 H); 3.33 – 2.98 (*m*, 2 H); 2.95 – 2.30 (*m*, 2 H); 1.97 – 1.80 (*m*, 2 H). HR-MS: 435.1728 ($[M+H]^+$, $C_{25}H_{26}N_2O_3S^+$; calc. 435.1742).

*4-[(1*H*-Indol-2-yl)carbonyl]-1-[(4-methylphenyl)methyl]-6-(2-phenylethyl)piperazin-2-one* (**33**, **A3B2C7**). IR: 3276, 2927, 1653, 1619, 1514, 1453, 1427, 1340, 1314, 1247, 1140, 1078, 970, 909, 806, 744, 703. ^{1}H-NMR ($CDCl_3$): 9.26 (br. *s*, 1 H); 7.68 (*d*, *J* = 7.8, 1 H); 7.43 (*d*, *J* = 8.4, 1 H); 7.36 – 7.01 (*m*, 9 H); 7.00 – 6.83 (*m*, 1 H); 6.95 (*d*, *J* = 7.8, 2 H); 5.28 (*d*, *J* = 14.6, 1 H); 5.08 – 4.65 (*m*, 2 H); 4.62 – 4.15 (*m*, 1 H); 3.74 (*d*, *J* = 14.6, 1 H); 3.38 – 2.40 (*m*, 4 H); 2.32 (*s*, 3 H); 1.99 – 1.77 (*m*, 2 H). HR-MS: 452.2343 ($[M+H]^+$, $C_{29}H_{29}N_3O_2^+$; calc. 452.2338).

4-[([1]Benzofuran-2-yl)carbonyl]-1-[(4-chlorophenyl)methyl]-6-(2-phenylethyl)piperazin-2-one (**33**, **A3B3C8**). IR: 2925, 1651, 1636, 1423, 1251, 1178, 1090, 1017, 809, 747, 700. ^{1}H-NMR ($CDCl_3$): 7.68 (*d*, *J* = 7.8,

1 H); 7.47 (*s*, 1 H); 7.42 (br. *t*, *J* = 7.3, 1 H); 7.36–6.97 (*m*, 9 H); 6.92 (*d*, *J* = 8.4, 2 H); 5.22 (*m*, 1 H); 5.12–4.71 (*m*, 2 H); 4.57–4.32 (*m*, 1 H); 3.68 (*d*, *J* = 14.6, 1 H); 3.30–2.31 (*m*, 4 H); 1.98–1.79 (*m*, 2 H). HR-MS: 473.1623 ($[M+H]^+$, $C_{28}H_{25}ClN_2O_3^+$; calc. 473.1632).

4-[([1]Benzothiophen-2-yl)carbonyl]-6-(2-phenylethyl)-1-{[3-(trifluoromethyl)phenyl]methyl}piperazin-2-one (**33**, **A3B4C9**). IR: 2925, 1646, 1631, 1459, 1412, 1324, 1246, 1163, 1116, 1069, 747, 700. ^{1}H-NMR ($CDCl_3$): 7.91–7.76 (*m*, 2 H); 7.57 (br. *s*, 1 H); 7.52 (br. *d*, *J* = 7.8, 1 H); 7.48–7.34 (*m*, 4 H); 7.33–6.96 (*m*, 6 H); 5.26 (*d*, *J* = 14.8, 1 H); 4.90–4.50 (*m*, 1 H); 4.81 (*d*, *J* = 18.1, 1 H); 4.44–4.18 (*m*, 1 H); 3.79 (*d*, *J* = 14.8, 1 H); 3.35–3.01 (*m*, 2 H); 3.00–2.29 (*m*, 2 H); 1.99–1.84 (*m*, 2 H). HR-MS: 523.1651 ($[M+H]^+$, $C_{29}H_{25}F_3N_2O_2S^+$; calc. 523.1667).

1-[(Furan-2-yl)methyl]-6-(2-phenylethyl)-4-(3-phenylprop-2-enoyl)piperazin-2-one (**33**, **A3B5C10**). IR: 2925, 1651, 1610, 1453, 1423, 1282, 1225, 1152, 1095, 1059, 1012, 971, 762, 700. ^{1}H-NMR ($CDCl_3$): 7.75 (*d*, *J* = 15.1, 1 H); 7.59–6.95 (*m*, 11 H); 6.85–6.68 (*m*, 1 H); 6.34–6.21 (*m*, 1 H); 6.19–6.02 (*m*, 1 H); 5.16–4.97 (*m*, 1 H); 4.92–4.65 (*m*, 1 H); 4.62–4.37 (*m*, 1 H); 4.32–4.16 (*m*, 1 H); 4.15–3.91 (*m*, 1 H); 3.55–3.25 (*m*, 1 H); 3.11–2.38 (*m*, 3 H); 1.98–1.68 (*m*, 2 H). HR-MS: 415.2018 ($[M+H]^+$, $C_{26}H_{26}N_2O_3^+$; calc. 415.2022).

The yields for all original library members (**33**, **A1B1C1**–**A3B5C10**, 150 compounds) are found in *Table 1*.

Secondary libraries (**33**, **A1B2C11**–**A1B2C110**, and **33**, **A1B3C111**–**A1B3C210**) were prepared from **20** and **21** (on a 6 and 8 µmol scale, resp.) according to the same general procedure described above. The deprotected secondary amines were coupled to carboxylic acids (**C11**–**C95** and **C111**–**C196**) with EDCI, EtN(i-Pr)$_2$. The chloroformate esters (**C96**–**C100** and **C197**–**C201**), sulfonyl chlorides (**C101**–**C105** and **C202**–**C206**), and isocyanates (**C106**–**C110** and **C207**–**C210**) were reacted with the deprotected amine hydrochloride salts of **20** and **21** with EtN(i-Pr)$_2$. Average yields for these couplings are found in *Table 4*. Representative samples were characterized (^{1}H-NMR, HR-MS) and indicated the desired product in excellent purity.

Luciferase Transcription Assays. SW480 Cells were plated at a density of 5×10^8 cells/100 mm plate. After 24 h, the cells were transfected with DNA (TOPFLASH or FOPFLASH, 6 µg and bluescript, 6 µg) with DOTAP according to the manufacturer's (*Boehringer Mannheim*) protocol. After an additional 24 h, the cells were seeded (8×10^4 cells/well) in 96-well plates (total media volume was 100 µl/well), and treated with 1 µl of a 1 mM DMSO soln. of each test compound (10 µM final concentration). Controls contained 1 µl of DMSO only. Luciferase activity was measured after 48 h, of incubation with the *Steady Glo Luciferase Kit* (*Promega*), according to the manufacturer's directions on a *Berthold Lumat LB9501* luminometer.

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