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Synthesis of Novel Furo, Thieno, and Benzazetoazepines and Evaluation of Their Cytotoxicity

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Abstract—We report the regio- and stereoselective synthesis of a novel *cis*-C_3N-C_4X-C_6N series (X = O, S, and C_2) from cyclic ketones. The cytotoxic activity of the new compounds was studied in five cell lines; the observed activities were in accordance with the concept of bioisosteric replacement.

Cancer remains a serious human health problem, despite considerable progress in the understanding of its biology and pharmacology. The main problem is that cancer is not one disease, but a group of diseases affecting different organs and systems of the body. Cancer develops due to abnormal and uncontrolled cell division, frequently at a rate greater than that of most normal body cells.[1] The traditional therapeutic strategies for the treatment of the cancer are surgery, radiotherapy, immunotherapy, and chemotherapy. Today, 50% of patients diagnosed with cancer are cured through one of these methods or by a combination of them. For some types of disseminated cancers, chemotherapy is the only effective therapy because it distributes anticancer drugs through the circulatory system.

We are currently engaged in a program aimed at synthesizing heterocyclic compounds with cytotoxic activity.[2] Recently, we described the regio- and stereocontrolled synthesis of the first members of the novel triheterocyclic system C_3N–C_4N–C_6N using as starting material the commercially available 5,5-dimethyl-1,3-cyclohexanedione.[3]

Compound **1** was sent to the National Cancer Institute for cytotoxic evaluation against a panel of 60 tumor cell lines. Compound **1** showed in vitro cytotoxic activity against breast tumor cell lines MCF7 and T-47D, but poor activity in vivo in antitumour hollow fibre studies.[4] These results prompted us to find the structural moieties responsible for the cytotoxic activity shown by **1**. Bioisosterism is a concept frequently used in drug design and development. The interesting results that have been obtained by studying bioisosteric compounds[5] led us to synthesize bioisosters of **1** by changing the pyrrole ring to a thiophene, a furan or a benzene ring, creating compounds **2**, **3**, and **4**, respectively. The cytotoxic activity of the new compounds was evaluated.

The synthetic route used to prepare compounds **2** and **3** is outlined in Scheme 1. The starting material 2-(2-oxopropyl)-1,3-cyclohexanodione (**5**) was synthesized according to our method described in the literature.[6] Treatment of **5** with Lawesson's reagent in a benzene/dimethoxyethane solution (2:1) afforded tetrahydrobenzofuran (**6**) and tetrahydrobenzothiophene (**7**) in 60 and 40% yields, respectively. Condensation of compound **6** (or **7**) with hydrochloride hydroxylamine, in the presence of 10% aqueous sodium hydroxide, in ethanol led to a *syn*/*anti* mixture of oximes **8** (or **9**). The regiospecific ring expansion of oxime **8** (or **9**) to the furoazepinone **10** (or **11**) was accomplished in polyphosphoric acid at 80–90 °C. Thereafter a heteroatomic interchange (O→S) and methylation gave the methylsulfanylimines **12** and **13**, respectively. Finally, cyclo-

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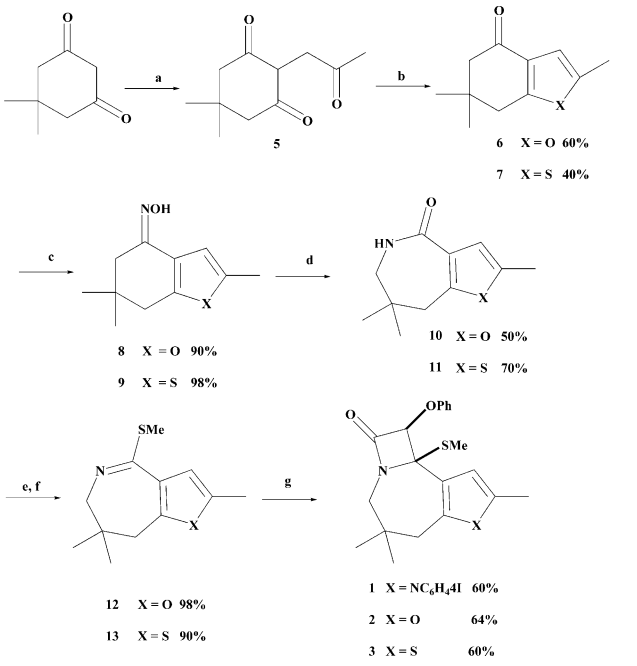
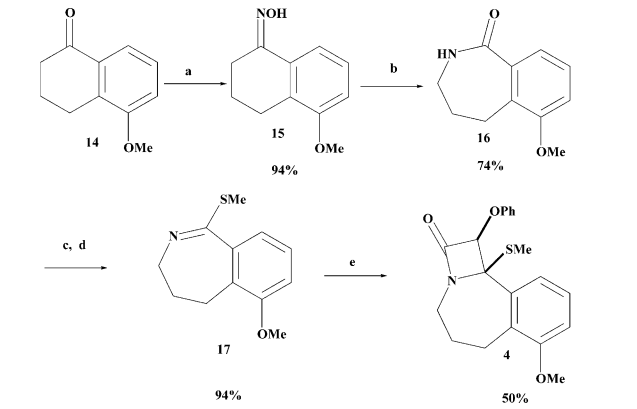


Scheme 1. (a) EtONa, CH_3COCH_2Cl, EtOH, reflux, 2 h, 70%; (b) Lawesson's reactive, C_6H_6/DME, reflux, 1 h; (c) $NH_2OH{\cdot}HCl$, NaOH aq, EtOH, 0.5 h, reflux; (d) APP, 80–90 °C, 3 h; (e) Lawesson's reactive, toluene, 2 h, reflux; (f) (i) CH_3I, CH_2Cl_2, rt, 1 h; (ii) $NaHCO_3$ aq; (g) $PhCH_2COCl$, Et_3N, C_6H_6, reflux, 8 h.



Scheme 2. (a) $NH_2OH{\cdot}HCl$, NaOH aq, EtOH, 0.5 h, reflux, 94%; (b) APP, 80 °C; (c) Lawesson's reactive, toluene, 2 h; reflux; (d) (i) CH_3I, CH_2Cl_2; (ii) $NaHCO_3$ aq; (e) $PhCH_2COCl$, Et_3N, C_6H_6, reflux, 12 h.

Table 1. The IC_{50} values (μM) of compounds **1**–**4** to the five cancer cell lines[a]

Compd	PC-3 (prostate)	U251 (CNS)	K562 (leukemia)	HCT-15 (colon)	MCF7 (breast)
1	87.0±8.6	40.0±3.6	>100	>100	>100
2	53.0±2.8	47.0±5.5	31.0±3.7	56.0±3.0	47.0±5.0
3	11.0±0.06	33.0±5.0	39.0±1.5	26.0±0.1	41.0±3.6
4	21.0±4.56	25.0±7.98	23.0±1.83	19.0±0.98	33.0±5.98
Doxorubicine	0.32±0.02	0.09±0.02	0.28±0.01	0.23±0.01	0.14±0.01

[a]The tumoral cell lines were supplied by the National Cancer Institute. The cytotoxicity assays were carried out at 5000–7500 cells/mL using the sulforhodamine B (SRB) protein assay to estimate cell growth. The percentage growth was evaluated spectrophotometrically in a Bio kinetics reader spectrophotometer.

addition of **12** and **13** with phenoxyacetyl chloride produced the *cis*-azetoazepinones **2** and **3**.

Following a similar reaction route (Scheme 2) compound **4** was prepared from 5-methoxy-α-tetralone **14** in good yield. All the compounds were purified either by recrystallization in hexane or by silica gel column chromatography.[8]

Azeto-pyrroloazepinone **1** and its bioisosteric derivatives **2**, **3**, and **4** were evaluated in vitro for their ability to inhibit growth of PC-3 prostate, U251 central nervous system, K562 leukemia, HCT-15 colon and MCF7 breast cells (Table 1).[7] Compound **1** displayed only moderate activity against the PC-3 (prostate) and U251 (CNS) cell lines. Compounds **2**, **3**, and **4** were found be active against every cell line.

The benzo derivative **4** proved to be the most active against all the cell lines tested with the exception of PC-3 prostate, for which the thiophene derivative **3** was the most active. Our results demonstrate that a bioisosteric modification of the pyrrole ring of compound **1** gives compounds with preserved cytotoxic activity. Moreover, this activity is enhanced by the presence of a benzene ring. Marked selectivity was found for thiophene derivative **3** on PC-3 prostate.

The preparation of compounds with structural modifications of molecules **4** and **3** is a matter for future investigation in our group, along with the evaluation of the cytotoxic properties of the synthesized compounds.

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8. Satisfactory spectroscopic and analytical data were obtained for all the new compounds; **1**, mp 194–195 °C; IR: 1759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3H), 0.96

(s, 3H), 1.89 (s, 3H), 2.14 (dd, 1H), 2.19 (s, 3H), 2.65 (d, 1H), 3.07 (d, 1H), 3.69 (dd, 1H), 5.50 (s, 1H), 5.80 (s, 1H), 6.80–7.80 (m, 9H). $C_{26}H_{27}IN_2O_2S$ requires: C, 55.91, H, 4.87; found: 55.98, H, 4.94. **2**, mp 103–108 °C; IR: 1761 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 3H), 1.09 (s, 3H), 2.16 (s, 3H), 2.19 (s, 3H), 2.62 (dd, 1H), 2.80 (d, 1H), 3.08 (dd, 1H), 3.72 (dd, 1H), 5.38 (s, 1H), 5.78 (s, 1H), 7.05–7.38 (m, 5H). $C_{20}H_{23}NO_3S$ requires: C, 67.20, H, 6.48; found: 67.28, H, 6.53. **3**, mp 135–138 °C; IR: 1760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 3H), 1.09 (s, 3H), 2.18 (s, 3H), 2.31 (s, 3H), 2.55 (dd, 1H), 3.01 (d, 1H), 3.12 (d, 1H), 3.76 (dd, 1H), 5.44 (s, 1H), 6.38 (d, 1H), 6.80–7.42 (m, 5H). $C_{20}H_{23}NO_2S_2$ requires: C, 64.30, H, 6.20; found: 64.28, H, 6.26. **4**, mp 110–111 °C; IR: 1762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.94 (m, 2H), 2.15 (s, 3H), 2.24 (dd, 2H), 2.44 (d, 1H), 3.60 (dd, 1H), 3.83 (s, 3H), 5.21 (s, 1H), 6.78 (d, 1H), 7.04 (d, 1H), 7.06 (dd, 1H), 7.21 (dd, 1H), 7.33 (dd, 1H), 7.37 (d, 1H); $C_{20}H_{21}NO_3S$ requires: C, 67.58, H, 5.96; found: 67.64, H, 6.04.