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Bioisosteric hybrids of two anti-inflammatory agents, rutaecarpine and piroxicam

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ABSTRACT

Bioisosteric replacements were accomplished by building the structural elements of piroxicam, an anti-inflammatory drug, into the pentacyclic system of rutaecarpine, a quinazolinocarboline alkaloid, in order to modify activity and selectivity on COX-isoenzymes. The pentacyclic compounds were synthesized efficiently by employing 1-oxo-9,10,11,12-tetrahydro-4*H*-pyrido[1,2-*b*]1,2-benzothiazine 5,5-dioxide as a key intermediate, and prepared by alternative routes. Condensation of the tricyclic ketone with arylhydrazines and subsequent Fischer-indolization provided the first representatives of new heterocyclic ring systems **3** and **4**.

New pharmacological results arising from active components of traditional Chinese folk medicines often provide promising lead structures for novel drug development.

Rutaecarpine **1** is a major quinazolinocarboline alkaloid isolated from the well-known Chinese herbal drugs Wu-Chu-Yu[1,2] and Shih-Hu,[3] the dried, unripe fruits of Rutaceous plants such as *Evodia rutaecarpa*[4] and *Evodia officinalis*. They have long been utilized for the treatment of inflammation-related symptoms[5,6] in traditional oriental medicinal practice in Japan and China.

According to an increasing number of reports, rutaecarpine **1** possesses a wide spectrum of pharmacological properties, such as calcitonin gene-related peptide (CGRP) mediated vasodilating, antihypertensive,[7] vasorelaxing,[8] antithrombotic,[9] antiplatelet,[10] antianoxic,[11] cardioprotective,[12] uterotonic,[13] antinociceptive,[14] analgesic,[4] diuretic,[4] specific 2,3,7,8-TCDD binding inhibitory,[15] and cytotoxic[16] activities. Recent studies have revealed that rutaecarpine **1** exhibits strong anti-inflammatory activity, and shows potent and selective inhibitory activity against COX-2 isoenzyme.[3,17]

Oxicams containing the 1,2-benzothiazine ring system are used as non-steroidal anti-inflammatory[18] drugs (NSAIDs). Examples such as 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamides, for example, piroxicam **2**, are applied widely in the treatment of rheumatoid arthritis. Piroxicam **2** acts by blocking the formation of prostaglandins through the nonselective inhibition of COX-1/2 isoenzymes.[19]

As part of our interest in developing safer anti-inflammatory drugs,[20] we describe the preparation of classical (quinazoline—benzothiazine; indole—7-azaindole) and nonclassical (amide moiety—pyrrole) bioisoster substituted[21] hybrid structures **3** and **4** obtained by combination of the structural elements of piroxicam **2** and the quinazolinocarboline skeleton **1** (Fig. 1). Through synthetic modifications of the pentacyclic ring system, the anti-inflammatory activity of **1** and its selectivity toward COX-2 can be modified

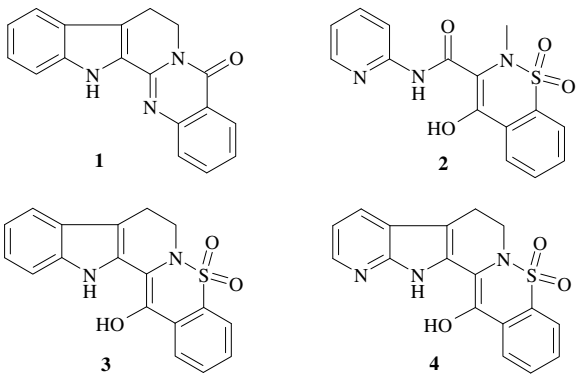

Figure 1. Hybrid structures **3** and **4** of rutaecarpine **1** and piroxicam **2**.

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and its undesired side effects eliminated. 11,12-Dichloro-rutaecarpine was recently been published as an example of a hybrid between rutaecarpine and bauerine C.[22]

The wide pharmacological activity of rutaecarpine **1** has led to the development of efficient methods for the total synthesis of rutaecarpine-type compounds.[23] We had earlier developed an original approach for the facile synthesis of rutaecarpine by B/C ring annelation,[23e,23g] and extended this approach to synthesize substituted derivatives of rutaecarpine in rings A, C, and E,[24] 1,2,3,4-tetrahydro derivatives, C-ring homologues,[25] C-ring opened analogues,[26] E-ring debenzo derivatives,[27] and 3-aza-[28] and 7-aza-bioisosters.[29]

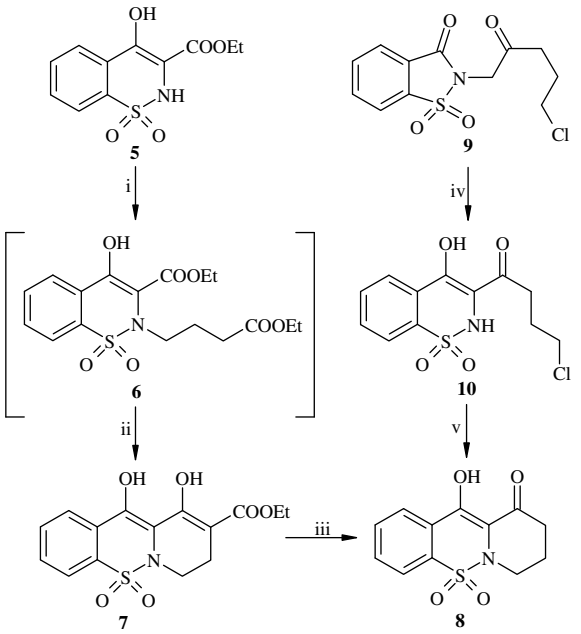
Tricyclic ketone **8** is described in the literature[30] and is prepared by alkylation of 2-acetylbenzothiadiazine with chloroacetaldehyde, following ring closure by condensation, then hydrogenation of the conjugated double bond with Pd-C catalyst. An alternative method for the synthesis of compound **8** was performed from the intermediate **5** of piroxicam[31] (Scheme 1). Alkylation of sulfonamide **5** with ethyl 4-chlorobutyrate was carried out in the presence of copper(II) carbonate, a complex forming agent,[31] to avoid O-alkylated product formation. Among the various bases and conditions investigated, the combination of NaOEt/EtOH/DMF led to the diester **6** in reasonable yield. Without isolation, **6** was transformed to tricyclic compound **7** via a consecutive Dieckmann-condensation catalyzed by excess sodium ethoxide in 47% yield. β-Keto-ester **7**, which existed in its enol form, was decarboethoxylated to afford 1-oxo-9,10,11,12-tetrahydro-4*H*-pyrido[1,2-*b*]1,2-benzothiazine 5,5-dioxide **8** in 81% yield. The reaction was carried out by heating **7** at 130 °C in DMSO solution in the presence of catalytic lithium chloride.

Tricyclic compound **8** was also prepared in satisfactory yield starting from commercially available saccharin and 1,5-dichloropentan-2-one in a one-pot procedure (alkylation, Gabriel–Colman rearrangement, and base catalyzed ring closure) under basic conditions using excess sodium ethoxide in anhydrous ethanol. Moisture plays a key role in the ring expansion step. The yield of the product decreases remarkably in the presence of traces of moisture in the alcohol and leads to the formation of undesired side products or a multicomponent gummy mixture. After the fast Gabriel–Colman rearrangement of **9** to **10**, copper(II) carbonate was added to the reaction mixture to exclude lactone formation by preventing O-alkylation with complex formation and to assure selective ring closure to linearly condensed tricyclic product **8**.

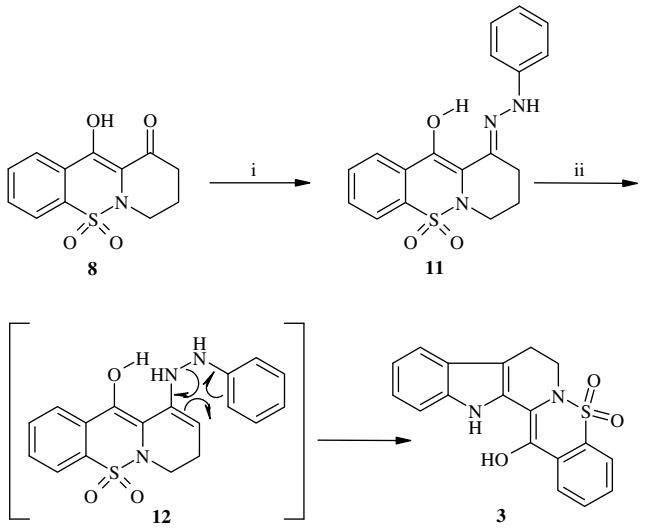
The pyridobenzothiazinone **8** was treated with phenylhydrazine in ethanol at 80 °C for 3 h to form hydrazone **11** in excellent yield (Scheme 2). Geometric isomerism around the C=N double bond is possible in **11**. NMR data showed only the existence of the *E* isomer containing an =N···H–O intramolecular H-bond. Phenylhydrazone **11** was subjected to Fischer indole synthesis as reported earlier.[23e] Thus, heating the hydrazone in polyphosphoric acid (PPA) at 180 °C for 30 min led, through **12**, to the pentacyclic compound **3** in 78% yield.[32]

The 7-azaindole derivative **4** can be considered a bioisoster of an indole moiety[33] and contains the 2-amino-pyridyl part of **2**. Contrary to indole, the 7-azaindole (1*H*-pyrrolo[2,3-*b*]pyridine) nucleus is only present in a few natural products such as alkaloids from the variolin family.[34] Nevertheless, many compounds of potential pharmaceutical interest containing the 7-azaindole motif[35] have been synthesized due to their improved physicochemical and pharmacological properties.

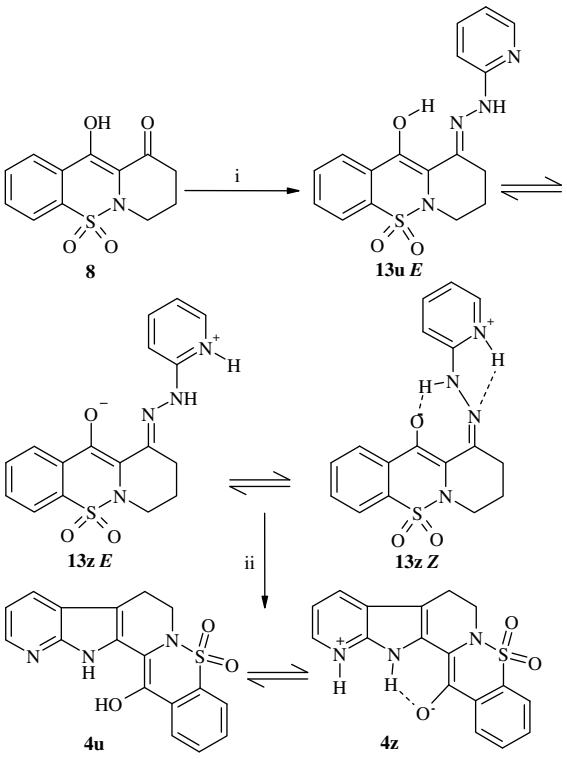
Condensation of the tricyclic ketone **8** with 2-pyridylhydrazine provided the 2-pyridylhydrazone **13** in 90% yield (Scheme 3). Compound **13** showed different geometric isomerism from the phenylhydrazone **11** due to its zwitterionic nature as identified from the upfield shift of the NH proton signals in its ^{1}H NMR spectrum. The unionized **13u *E*** isomer is in equilibrium with the seven- and five-membered H-bond stabilized and sterically unfavorable **13z *Z*** isomer in chloroform (isomer ratio = 14:86). Solvent dependent geometric isomerism exists in more polar solvents. The **13z *E*:13z *Z*** isomer ratio proved to be 68:32 in DMSO-d_6 (δ = 13.49 (s, 0.68H, NH_E), 15.67 (s, 0.32H, NH_Z), 14.32 (br s, 1H, NH^+)). Fischer-indolization of pyridylhydrazone **13** was performed in PPA at 180 °C for 1 h to give 7-azaindolopyridoquinazoline **4** as a novel heterocyclic ring system in moderate yield (57%).[36] The pyridine nitrogen in the A-ring of compound **4** is protonated by the acidic enolic hydroxyl group, and the enolate forms a strong intramolecular hydrogen bond with the indole NH. The highly stable zwitterionic form **4z** is the major species in equilibrium with the



Scheme 1. Synthesis of 1-oxo-9,10,11,12-tetrahydro-4*H*-pyrido[1,2-*b*]1,2-benzothiazine 5,5-dioxide **8**. Reagents and conditions: (i) Cl–$(CH_2)_3$–COOEt, NaOEt/EtOH, $CuCO_3$, DMF; (ii) NaOEt/EtOH, DMF, 65 °C, 8 h (47%); (iii) LiCl, DMSO, 130 °C, 3 h (81%); (iv) NaOEt/EtOH, 80 °C, 40 min; (v) NaOEt/EtOH, $CuCO_3$, DMF, 70 °C, 5 h (42%).



Scheme 2. Synthesis of indolopyrido-1,2-benzothiazine 5,5-dioxide **3**. Reagents and conditions: (i) Ph–$NHNH_2$, EtOH, 80 °C, 3 h (94%); (ii) PPA, 180 °C, 30 min (78%).



Scheme 3. Synthesis of 12-azaindolopyrido-1,2-benzothiazine 5,5-dioxide **4**. Reagents and conditions: (i) 2-$NHNH_2$–C_5H_4N, EtOH, 80 °C, 5 h (90%); (ii) PPA, 180 °C, 1 h (57%).

unionized form **4u.** The ionization process is similar to oxicam protonation,[37,38] as published earlier by us, but the characteristic dynamic structural features of oxicam **2** are abolished by the highly conjugated, rigid pentacyclic structure.

In conclusion, a short and efficient synthesis has been developed for bioisosteric analogues **3** and **4** of rutaecarpine **1** by building the pharmacophoric structural elements of piroxicam **2** into the pentacyclic system of the alkaloid. These hybrid structures were prepared in two alternative routes in five or preferably three synthetic steps. The synthesized pentacylic compounds **3** and **4** are the first representatives of new heterocyclic ring systems.

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32. Compound **3**: Mp: 238–241 °C. UV: in EtOH λ_{max} (log ε: 379. 4.30), 374 (4.42), 362 (4.32), 328 (3.86), 296 (3.80), 226 (4.41) nm. ^{1}H NMR (600 MHz, DMSO-d_6, Aldrich) δ 3.21 (t, J = 7.0 Hz, 2H), 4.25 (t, J = 7.0 Hz, 2H), 7.12 (ddd, J = 1.0, 7.9, 8.0 Hz, 1H), 7.30 (dd, J = 1.2, 7.9, Hz, 1H), 7.49 (dd, J = 1.0, 7.1 Hz, 1H), 7.67 (dd, J = 1.2, 7.9 Hz, 1H), 7.71 (ddd, J = 1.2, 8.0, 8.2 Hz, 1H), 7.77 (ddd, J = 1.3, 7.1, 8.0 Hz, 1H), 7.84 (dd, J = 1.3, 8.2 Hz, 1H), 8.10 (dd, J = 1.2, 7.1 Hz, 1H), 10.67 (s, 1H, OH), 12.26 (s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ 22.31, 40.17, 105.5, 112.3, 119.1, 119.6, 119.7, 122.2, 122.4, 124.3, 125.0, 126.9, 129.9, 131.9, 135.8, 138.4, 143.9, 135.3. HRMS (ESI): calcd for $(M+H)^+$ ($C_{18}H_{15}N_2O_3S$) requires m/z 339.0803, found 339.0812.
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36. Compound **4**: Mp: 289–291 °C. UV: in EtOH λ_{max} (log ε: 390 (4.27), 385 (4.38), 373 (4.28), 334 (3.91), 218 (4.41) nm. ^{1}H NMR (600 MHz, DMSO-d_6, Aldrich) δ 3.23 (t, J = 6.8 Hz, 2H), 4.18 (t, J = 6.8 Hz, 2H), 7.04 (dd, J = 7.7, 4.8 Hz, 1H), 7.73 (ddd, J = 1.2, 8.0, 8.2 Hz, 1H), 7.75 (ddd, J = 1.3, 7.1, 8.0 Hz, 1H), 7.87 (dd, J = 7.7, 1.7 Hz, 1H), 7.98 (dd, J = 1.3, 8.2 Hz, 1H), 8.25 (dd, J = 4.8, 1.7 Hz, 1H), 8.33 (dd, J = 1.2, 7.1 Hz, 1H), 10.89 (s, 1H, NH), 13.38 (s, 1H, NH), 14.32 (s, 1H, H-bonded NH).13C NMR (150 MHz, DMSO-d_6) δ 22.3, 42.1, 103.7, 119.8, 120.8, 123.1, 124.3, 127.5, 127.8, 128.6, 130.4, 131.6, 136.5, 142.5, 145.5, 146.5, 134.8. HRMS (ESI): calcd for $(M+H)^+$ ($C_{17}H_{14}N_3O_3S$) requires m/z 340.0755, found 340.0760.
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