# Syntéza derivátů karboxyxanthonu jako stavebních bloků pro enantiomerně čisté sloučeniny.

Syntéza a stanovení struktury derivátu xanthonu (XD) 2-karboxy-6-methoxyxanthonu (XD-2).

---

# Synthesis of carboxyxanthone derivatives as building blocks for enantiomeric pure compounds.

Synthesis and structure elucidation of xanthone derivative (XD) 2-carboxy-6-methoxyxanthone (XD-2)

Project I 2010/2011

**Author**: Jana Heczková

**Advisor**: Professora Doutora Madalena Maria de Magalhães Pinto

Assoc. Prof. RNDr. Veronika Opletalová, Ph.D.

This is to declare that this diploma thesis is my own work and I worked on it on my own. All literature sources are properly cited in reference list.

Date: Signature:

# Acknowledgements

**Index**

# Abstract

The importance of xanthone derivatives is considerable. They possess large variety of biological and pharmacological activities. Many of them proved to be important building blocks for synthesis of new compounds.

Chirality is a fundamental property of biological systems and reflects the underlying asymmetry of matter. Almost one-third of all drug sales worldwide are chiral compounds and the authorities recommend that the chiral drugs should be saled in pure enantiomeric forms because enantiomers may differ both quantitatively and qualitatively in their biological activities. At one extreme, one enantiomer may be devoid of any biological activity; at the other extreme, both enantiomers may have qualitatively different biological activities. Enantiomers also differ in bioavailability – one enantiomer can be more bioavailable than the other, also the volume of distribution is different for *levo* and *dextro* enantiomer.

The synthesis of the xanthone derivative (XD) 2-carboxy-6-methoxyxanthone was a six-step reaction:

1. Synthesis of dimethyl 4-bromoisophthalate by Fisher esterification.
2. *N,N*-Dimethylglycine-promoted Ullmann condensation of dimethyl 4-bromoiso-phthalate with 3-methoxyphenol to get dimethyl 4-(3'-methoxyphenoxy) isophthalate.
3. Hydrolysis of dimethyl 4-(3'-methoxyphenoxy)isophthalate to obtain 4-(3'-methoxyphenoxy)isophthalic acid.
4. Synthesis of 2-carboxy-6-methoxyxanthone and 2-carboxy-8-methoxyxanthone by an intramolecular acylation.
5. Esterification of 2-carboxy-6-methoxyxanthone and 2-carboxy-8-methoxy-xanthone.
6. Hydrolysis of methyl 6-methoxyxanthone-2-carboxylate to obtain 2-carboxy-6-methoxyxanthone.

2-Carboxy-6-methoxyxanthone was used as a building block for synthesis of an enantiomerically pure compound, namely *N*-[(1*R*)-1-(hydroxymethyl)-2-methylpropyl]-

6-methoxyxanthone-2-carboxamide by a coupling reaction with the amino alcohol D-valinol.

Almost all the synthesized compounds were structurally elucidated by different spectroscopic methods: $^1$H and $^{13}$C Nuclear Magnetic Resonance (NMR) and by Infrared Spectroscopy (IR).

# Abstrakt

Důležitost derivátů xanthonu je nesporná. Mají širokou škálu biologických a farmakologických účinků. Mnoho z nich se stalo důležitými stavební bloky pro syntézu nových sloučenin.

Chiralita je základní vlastností biologických systémů a odráží základní asymetrie hmoty. Téměř jedna třetina prodeje všech léků po celém světě jsou chirální sloučeniny a autority doporučují, aby chirální léky byly prodávány pouze v čistých enantiomerních formách. Důvodem je, že se enantiomery mohou lišit kvantitativně i kvalitativně v jejich biologické aktivitě. V prvním extrému, může jeden enantiomer postrádat biologickou aktivitu, v opačném extrému, mohou mít oba enantiomery kvalitativně odlišné biologické aktivity. Enantiomery se také liší v biologické dostupnosti – jeden enantiomer může být více biologicky dostupný než ostatní, i distribuční objem je jiný pro *levo* a jiný pro *dextro* enantiomer.

Syntéza derivátu xanthonu (XD) 2-karboxy-6-methoxyxanthonu zahrnovala šest reakčních kroků:

1. Syntéza dimethyl-4-bromoisoftalátu Fisherovou esterifikací.
2. Ullmannova kondenzace dimethyl-4-bromisoftalátu s 3-methoxyfenolem podporovaná *N,N*-dimethylglycinem za vzniku dimethyl-4-(3'-methoxyphenoxy) isoftalátu.
3. Hydrolýza dimethyl 4-(3'-methoxyphenoxy)isoftalátu.
4. Syntéza 2-karboxy-6-methoxyxanthonu a 2-karboxy-8-methoxyxanthonu intramolekulární acylací.
5. Esterifikace 2-karboxy-6-methoxyxanthonu a 2-karboxy-8-methoxyxanthonu.
6. Hydrolýza methyl-6-methoxyxanthon-2-karboxylátu za vzniku 2-karboxy-6-methoxyxanthonu.

2-karboxy-6-methoxyxanthon byl použit jako stavební blok pro syntézu enantiomerně čisté sloučeniny, jmenovitě *N*-[(1*R*)-1-(hydroxymethyl)-2-methylpropyl]-6-methoxyxanthon-2-karboxamidu, který byl syntetizován spojením 6-methoxyxanthon-2-karboxylátu s aminoalkoholem D-valinolem.

Skoro všechny připravené sloučeniny byly strukturně charakterizované různými spektroskopickými metodami: $^{1}$H NMR and $^{13}$C NMR (nukleární magnetickou rezonancí) a IR (infračervenou spektroskopií).

# Abbrevitations and symbols

$^{13}$C NMR = carbon nuclear magnetic resonance

$^{1}$H NMR = proton nuclear magnetic resonance

AMP = adenosine monophosphate

CEQUIMED-UP = Centro de Química Medicinal da Universidade do Porto

$CDCl_3$ = deuterated chloroform

CNS = central nervous system

$\delta$ = chemical shift

*d* = doublet

*dd* = double doublet

DMSO-$d_6$ = dimethyl-$d_6$ sulfoxide

Hz = hertz

IR = infrared spectroscopy

*J* = coupling constant

*M* = multiplet

MAO = monoamine oxidase

MeOH= methanol

MHz = megahertz

MP = melting point

ppm = parts per million

QSAR = quantitative structure-activity relationship

*s* = singlet

SAR = structure-activity relationship

*t* = triplet

TBTU = *O*-(benzotriazol-1-yl)-*N*, *N*, *N'*, *N'*-tetramethylluronium tetrafluoroborate

THF = tetrahydrofuran

TLC = thin layer chromatography

TNF = tumor necrosis factor

UV = ultraviolet

$\nu_{max}$ = maximal frequency

XD = xanthone derivative

# 1. INTRODUCTION

## 1.1. Xanthones generally

The xanthones or *9H*-xanthen-*9*-ones (**Fig. 1**) comprise an important class of oxygenated heterocycles. The term xanthone (from the Greek ξαυθός (xanthos), meaning yellow, designates heterocyclic compounds having a dibenzo-γ-pyrone skeleton as basic structure. Natural xanthones can be subdivided, depending on the nature of the substituents in the dibenzo-γ-pyrone scaffold, into six main groups: simple oxygenated xanthones (mono, di, tri, tetra, penta and hexaoxygenated), glycosylated xanthones, prenylated xanthones and their derivatives, xanthonolignoids, bis-xanthones and miscellaneous. On the other hand, xanthones of synthetic origin can have simple groups such as hydroxyl, methoxyl, methyl, carboxyl, as well as more complex substituents such as epoxide, azole, methylidenebutyrolactone, aminoalcohol, sulfamoyl, methylthiocarboxylic, and dihydropyridine in their scaffold. [1-4]
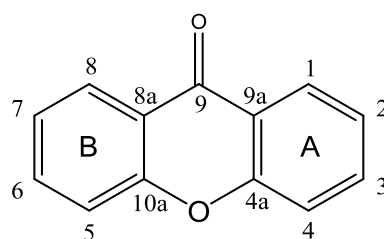


**Fig. 1** Xanthone nucleus and numbering

A number of xanthone derivatives are secondary plant metabolites and have been isolated from several natural sources like lichens, fungi, microorganisms and a few higher plants, mainly belonging to Anacardiaceae (*Mangifera*), Guttiferae (*Garcinia, Platonia*) and Gentianaceae (*Gentiana, Swertia*) families. All these oxygenated heterocyclic derivatives possess a structural relationship to other γ-pyrone natural products, namely flavonoids and chromones and have attracted, over the years, medicinal chemist's interest, because of their diverse pharmacological properties. [2-7]

## 1.2. Xanthones and their biological activity

Pharmacological investigations of xanthones date back to 1968, when Bhattacharya's group reported the diuretic and cardiotonic actions of the natural glycoside mangiferin. [8] Since that many other biological activities for xanthone derivatives has been described, and several pharmacological studies were carried out. [5,6,9] Some structure-activity relationship (SAR) studies have recently been described for the following activities: tuberculostatic, antimycotic, antimalarial, antiplatelet, antithrombotic, anti-inflammatory, anticonvulsant, antiallergic, antitumor, antimutagenic, and antioxidant. Furthermore, SAR studies have been also developed in the field of adrenergic blocking agents, calcium antagonists, P-glycoprotein modulators, leukotriene LTB4 receptors blocking agents, as well as for effects on several enzymes, such as acetylcholinesterase, aldose reductase, aromatase, cAMP phosphodiesterase, human cytochrome P450 17-α-hydroxylase-17,20-lyase, monoamine oxidase (MAO), sphingomyelinases, and protein kinases. [1]

From the available SARs, quantitative structure-activity relationship (QSAR) studies are emerging for tuberculostatic agents and MAO inhibitors. More recently, computational studies have been developed in the field of antimalarial agents using docking studies to obtain a correlation between xanthone derivatives and hematin/hemazoin targets. [1,7]

As phenolic compounds, xanthones have been reported for their antioxidant properties. They can act as metal chelators, free radical scavengers, as well as inhibitors of lipid peroxidation. These properties have been implicated in their hepatoprotective, anti-inflammatory and cancer chemopreventive actions. [1,7]

The *in vitro* inhibitory activity of xanthones on tumor cell lines is remarkable. They can act on wide range of tumor cell lines, like leukemia, multiple myeloma, oral squamous cell carcinoma, melanoma, colon carcinoma, breast adenocarcinoma, ovarian carcinoma, uterine carcinoma, prostate carcinoma, lung carcinoma, liver carcinoma, stomach carcinoma, renal carcinoma, pancreatic carcinoma, central nervous system (CNS) carcinoma, glioma, colorectal carcinoma, hepatoma, bladder carcinoma, neuroblastoma, pheochromocytoma, adrenocortical carcinoma, fibroblasts tumor cells,

fibrosarcoma, epithelial tumor cells, nasopharynx epidermoid carcinoma and further more. Also *in vivo* studies have been carried out for example in colon adenocarcinoma, lymphocytic leukemia, ovarian carcinoma, melanoma, pancreatic carcinoma, sarcoma, glioma and further more. [1]

## 1.2.1. 5,6-Dimethylxanthenone-4-acetic acid (DMXAA)

DMXAA (**Fig. 2**) is an anticancer drug with an unusual mechanism of action compared with conventional cytotoxic anticancer drugs. DMXAA induces rapid vascular collapse and necrosis in transplantable murine tumours, thought to be due to immune modulation and the induction of cytokines, in particular TNF-$\alpha$, interferons, serotonin and nitric oxide. Co-administration of DMXAA with other drugs has been shown to result in enhanced antitumour activity and alterations in pharmacokinetics, as reported for the combination of DMXAA with melphalan, thalidomide, and the bioreductive agent tirapazamine, in mouse models. DMXAA is metabolized by glucuronidation that is catalyzed by uridine diphosphate glucuronosyltransferases and cytochrome P450 (CYP1A2). [1,10-13]
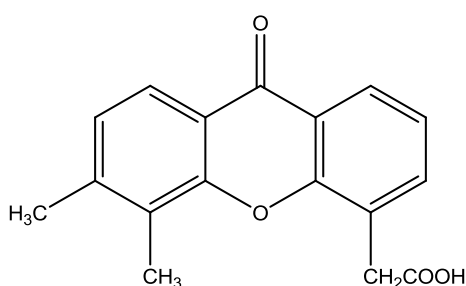


**Fig. 2** DMXAA

## 1.2.2. Psorospermin

Psorospermin (**Fig. 3**) is a natural dihydrofuranoxanthone, isolated from the roots and bark of a tropical African plant *Psorospermum febrifugum* (Guttiferae), in advanced preclinical development. This natural product was shown to have both *in vitro* and *in vivo* (in mice models) antileukaemic activity and to be active against several

12

human tumor cell lines from different tumor types such as breast, colon, lymphocytic leukemia, drug-resistant leukemias, and in AIDS-related lymphoma. Psorospermin acts by the intercalation into the DNA molecule and by the guanin alkylation at the topoisomerase II cleavage site. [1,6,14]
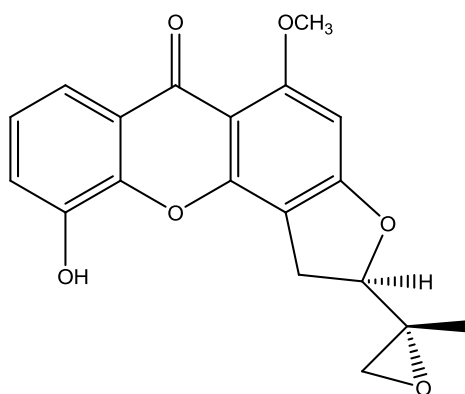


**Fig. 3** Psorospermin

### 1.2.3. Mangiferin

Mangiferin, 1,3,6,7-tetrahydroxyxanthone-2-C-ß-*D*-glucopyranosyl (**Fig. 4**), is a widely distributed polyphenol in higher plants (*Mangifera indica, Salacia reticulata, Cratoxylum cochinchinensis, Polygala elongata*) and is well-known for its antioxidant, anti-inflammatory, immunomodulatory, antidiabetic, antitumor, antibacterial, anti-HIV and antiviral effects. Interestingly, mangiferin was the first xanthone to be investigated for pharmacological purposes. In Cuba, mangiferin is traditionally used as an anti-inflammatory, analgesic and also as an antioxidant under brand name Vimang. In Sri Lanka, mangiferin has been used in the obesity treatment and particularly for diabetes type II under brand name Salaretin. [1,15,16]
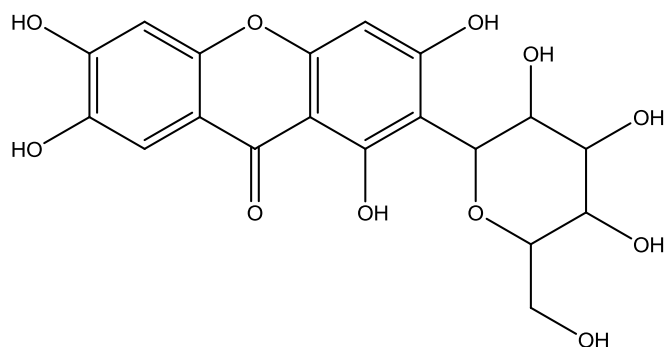
**Fig. 4** Mangiferin

## 1.2.4. Mangosteen

*Garcinia mangostana* L. (Clusiaceae) is commonly known as mangosteen and "mangkhut", and its fruits (**Fig. 5**) are referred to, in Thailand, as the "queen of fruits", as a result of its delicious taste. The mangosteen plant grows slowly to 7 – 12 m high. The pericarps of mangosteen have been used for many years in traditional medicine for the treatment of skin infection, diarrhea, dysentery, inflammation, cancer (leukemia, hepatocellular carcinoma, gastric, breast and lung tumor), ulcers and wounds. The extract of *Garcinia mangostana* L. contains prenylated and glycosyl prenylated mangostins such as α-mangostin (**Fig. 6**), γ-mangostin (**Fig. 7**) and other compounds. [1,17]
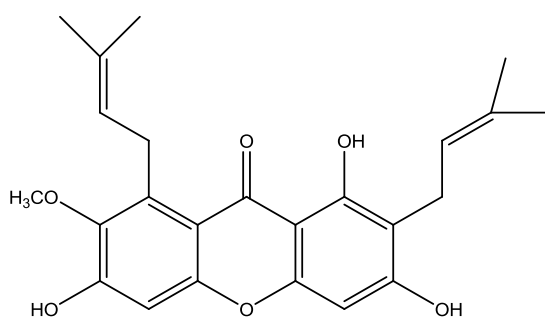


**Fig. 5** Mangosteen fruits (see http://www.greenquest.co.uk/Thaibiz.html)
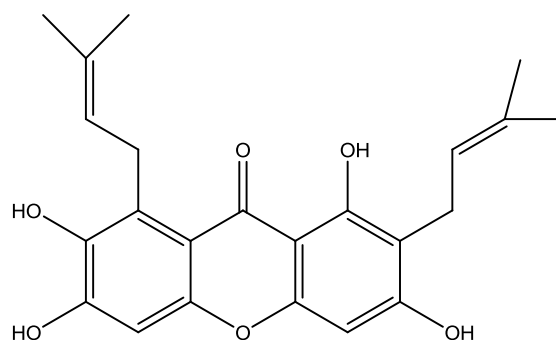
**Fig. 6** α-mangostin

**Fig. 7** γ-mangostin

# 1.3. Chirality

Chirality is a fundamental property of biological systems and reflects the underlying asymmetry of matter. The molecules that are not superimposable with its own image in the mirror and, then, exist in two enantiomeric forms, are considered chiral. These enantiomers are optical stereoisomers, because they possess optical activity. The simplest model for a chiral molecule is the carbon atom linked to four different groups. Such carbons are designated as stereogenic, assymetrical or chirality centers. Compounds that contain both mirror-image enantiomers in equal proportions are referred to as racemic mixtures or racemates. It is important to point out that enantiomers have the same physical and chemical properties, such as solubility or melting point. The two enantiomeric forms can be distingued by their optical activity, which consists in the property of rotating the plane of polarized light.

The conventions that have been used to designate the enantiomers are *R* and *S* according to Cahn, Ingold and Prelog (more systematic, universaly used), and D and L, used in molecules of biochemic importace like sugars and amino acids. The symbols (+) or *d* for dextrorotatory and (-) or *l* for levorotatory designate optical rotation. [19-21]

Many biological events involve proteins with asymmetry originated by the intrinsic chirality of the fundamental building blocks – the L-amino acids. In broad sense drug receptor interactions have long been known to be stereoselective. Enantiomers may

differ both quantitatively and qualitatively in their biological activities. At one extreme, one enantiomer may be devoid of any biological activity; at the other extreme, both enantiomers may have qualitatively different biological activities. These stereoselective differences may arise not only from drug interactions at pharmacological receptors, but also from pharmacokinetic events, including protein binding, metabolism and transport. [22]

Active transport processes may discriminate between the enantiomers, with implications in bioavailability – one enantiomer can be more bioavailable than the other, also the volume of distribution is different for *levo* and *dextro* enantiomer. Drug metabolizing enzyme systems are also subject to stereoselective influences. Two isomers of a drug are often metabolized at different rates. This may result in accumulation of the inactive enantiomer or rapid elimination of the active one and vice versa. Two isomers of a drug also induce or inhibit the cytochrome enzymes stereoselectively.

The potential advantages of using enantiomeric pure drugs are:

- less complex, more selective pharmacodynamic profile
- potential for an improved therapeutic index
- less complex pharmacokinetic profile
- reduced potential for complex drug interactions
- less complex relationship between plasma concentration and effect. [24]

A number of general reviews are available outlining stereoselectivity in both drug action and disposition and also giving some possible advantages of single enantiomers of a range of agents including antimalarial drugs, bronchodilators, β-blockers, psychoactive drugs, antiarrhytmic, anaesthetic and anti-asthma agents. [25-29]

# 2. OBJECTIVES AND PLANNING

Xanthones are a group of compounds with very important biological activities. Many of them are important building blocks for further synthesis of new interesting compounds. The group in the Faculty of Pharmacy of UP (CEQUIMED-UP) has a vast experience in synthesis and structure elucidation of XDs.

The aims of this work are

- **Synthesis** of the xanthone derivative 2-carboxy-6-methoxyxanthone using a six-step reaction.
- **Synthesis** of the chiral xanthone derivative *N*-[(1*R*)-1-(hydroxymethyl)-2-methylpropyl]-6-methoxyxanthone-2-carboxamide, by coupling 2-carboxy-6-methoxyxanthone with the amino alcohol D-valinol.
- **Structure elucidation** of the synthesized compounds by spectroscopic methods (IR, $^1$H NMR, $^{13}$C NMR).

# 3. RESULTS AND DISCUSSION

Results and discussion have been included into Attachment due to confidential reasons.

# 4. EXPERIMENTAL PART

Experimental procedures have been included into Attachment due to confidential reasons.

# 5. CONCLUSIONS

A number of compounds were successfully synthesized in this work:

➢ Dimethyl 4-bromoisophthalate **(2)**: 10.98 g, 60%

➢ Dimethyl 4-(3'-methoxyphenoxy)isophthalate **(4)**: 0.28 g, 25% and 6.3273 g, 54%

➢ 4-(3'-Methoxyphenoxy)isophthalic acid **(5)**: 4.95 g, 83%

➢ 2-Carboxy-6-methoxyxanthone **(6)**: 3.51 g, 94%

➢ Methyl 6-methoxyxanthone-2-carboxylate **(8)**: 4.02 g

➢ *N*-[(1*R*)-1-(Hydroxymethyl)-2-methylpropyl]-6-methoxyxanthone-2-carboxamide **(10)**: 0.72 g, 75%.

The structures of the compounds **2, 4, 5, 6, 8, 10** were successfully elucidated using several spectroscopic methods, namely IR, $^1$H NMR, $^{13}$C NMR.

In 2011, similar compound have been patented as builging blocks for the preparation of chiral stationary phases. [30]

# 6. REFERENCES

1. PINTO, M. M. M.; SOUSA, M. E.; NASCIMENTO, M. S. J. Xanthone derivatives: new insights in biological activities. *Curr. Med. Chem.* **2005**, *12*, 2517-2538.

2. PERES, V.; NAGEM, T. J.; DE OLIVEIRA, F. F. Tetraoxygenated naturally occurring xanthones. *Phytochemistry.* **2000**, *55*, 683-710.

3. VIEIRA, L. M. M.; KIJJOA, A. Naturally-occurring xanthones: recent developments. *Curr. Med. Chem.* **2005**, *12*, 2413-2446.

4. EL-SEEDI, H. R.; EL-GHORAB, D. M.; EL-BARBARY, M. A.; ZAYED, M. F.; GÖRANSSON, U.; LARSSON, S.; VERPOORTE, R. Naturally occurring xanthones; latest investigations: isolation, structure elucidation and chemosystematic significance. *Curr. Med. Chem.* **2009**, *16,* 2581-2626.

5. FOTIE, J.; BOHLE, D. S. Pharmacological and biological activities of xanthones. *Anti-Infect. Agents Med. Chem.* **2006**, *5*, 15-31.

6. POULI, N. ; MARAKOS, P. Fused xanthone derivatives as antiproliferative agents. *Anti-Cancer Agents Med. Chem.* **2009**, *9*, 77-98.

7. MARONA, H.; SZKARADEK, N.; RAPACZ, A.; FILIPEK, B.; DYBAŁA, M.; SIWEK, A.; CEGŁA, M.; SZNELER, E. Preliminary evaluation of pharmacological properties of some xanthone derivatives. *Bioorg. Med. Chem.* **2009**, *17*, 1345-1352.

8. FINNEGAN, R. A.; STEPHANI, G. M.; GANGULI, G.; BHATTACHARYA, S. K. *J. Pharm.Sci.* **1968**, *18*, 718.

9. GIRI, R.; GOODELL, J. R.; XING, C.; BENOIT, A.; KAUR, H.; HIASA, H.; FERGUSON, D. M. Synthesis and cancer cell cytotoxicity of substituted xanthenes. *Bioorg. Med. Chem.* **2010**, *18,* 1456-1463.

10. ZHOU, S.; CHIN, R.; KESTELL, P.; TINGLE, M. D.; PAXTON, J. W. Effects of anticancer drugs on the metabolism of the anticancer drug 5,6-dimethylxanthenone-4-acetic (DMXAA) by human liver microsomes. *Br. J. Clin. Pharmacol.* **2001,** *52*, 129-136.

11. CHUNG, F.; LIU, J.; CHING, L. M.; BAGULEY, B. C. Consequences of increased vascular permeability induced by treatment of mice with 5,6-dimethylxanthenone-4-acetic acid (DMXAA) and thalidomide. *Cancer Chemother. Pharmacol.* **2008**, *61*, 497-502.

12. ZHOU, S. F.; PAXTON, J. W.; TINGLE, M. D.; KESTELL, P.; JAMESON, M. B.; THOMPSON, P. I.; BAGULEY, B. C. Identification and reactivity of the major metabolite (beta-1-glucuronide) of the anti-tumour agent 5,6-dimethylxanthenone-4-acetic acid (DMXAA) in humans. *Xenobiotica*. **2001**, *31*, 277-293.

13. ZHOU, S. F.; KESTELL, P.; PAXTON, J. W. Predicting pharmacokinetics and drug interactions in patients from in vitro and in vivo models: the experience with DMXAA, an anti-cancer drug eliminated mainly by conjugation. *Drug Metab. Rev.* **2002**, *34*, 751–790.

14. NGUYEN, Q. C.; NGUYEN, T. T.; YOUGNIA, R.; GASLONDE, T.; DUFAT, H.; MICHEL, S.; TILLEQUIN, F. Acronycine derivatives: a promising series of anticancer agents. *Anticancer Agents Med. Chem.* **2009**, *9,* 804-815.

15. ZHANG, H.; HOU, Y.; LIU, Y.; YU, X.; LI, B.; CUI, H. Determination of mangiferin in rat eyes and pharmacokinetic study in plasma after oral administration of mangiferin-hydroxypropyl-beta-cyclodextrin inclusion. *J. Ocul. Pharmacol. Ther.* **2010,** *26*, 319-324.

16. SINGH, S. K.; KUMAR, Y.; KUMAR, S. S.; SHARMA, V. K.; DUA, K.; SAMAD, A. Antimicrobial evaluation of mangiferin analogues. *Indian J. Pharm. Sci.* **2009**, *71*, 325-328.

17. CHIN, Y. W.; KINGHORN, A. D. Structural characterization, biological effects, and synthetic studies on xanthones from mangosteen (*Garcinia mangostana*), a popular botanical dietary supplement. *Mini-Rev. Org. Chem.* **2008**, *5,* 355-364.

18. JARIMOPAS, B.; PUSHPARIKSHA, P.; SINGH, S. P. Postharvest damage of mangostan and quality fading using mechanical and optical properties as indicators. *Int. J. Food Prop.* **2009,** *12*, 414–426.

19. BURKE, D.; HENDERSON, D. J. Chirality: a blueprint for the future. *Br. J. Anaesth.* **2002**, *88*, 563-76.

20. LE GUENNEC, P. Two-dimensional theory of chirality. I. Absolute chirality. *J. Math. Phys.* **2000**, *41*, 5954–5985.

21. HOWLAND, R. H. Understanding chirality and stereochemistry: three-dimensional psychopharmacology. *J. Psychosoc. Nurs. Ment. Health. Serv.* **2009**, *47*, 15-18.

22. TRIGGLE, D. J. Stereoselectivity of drug action. *Drug Discov. Today*. **1997**, *2*, 138-147.

23. PATIL, P. A.; KOTHEKAR, M. A. Development of safer molecules through chirality. *Indian J. Med. Sci.* **2006**, *60*, 427-437.

24. HUTT, A. J.; VALENTOVÁ, J. The chiral switch: the development of single enantiomer drugs from racemates. *Acta Facult. Pharm. Univ. Comenianae*. **2003**, *50*, 7-23.

25. BROCKS, D. R.; MEHVAR, R. Stereoselectivity in the pharmacodynamics and pharmacokinetics of the chiral antimalarial drugs. *Clin. Pharmacokinet*. **2003**, *42*, 1359-1382.

26. RANADE, V. V.; SOMBERG, J. C. Chiral cardiovascular drugs. *Am. J. Ther.* **2005**, *12*, 439–459.

27. MEHVAR, R.; BROCKS, D. R.; VAKILY, M. Impact of stereoselectivity on the pharmacokinetics and pharmacodynamics of antiarrhythmic drugs. *Clin. Pharmacokinet*. **2002**, *41*, 533-558.

28. MEHVAR, R.; BROCKS, D. R.; VAKILY, M. Stereospecific pharmacokinetics and pharmacodynamics of beta-adrenergic blockers in humans. *J. Pharm. Sci.* **2001**, *4*, 185-200.

29. BAKER, G. B.; PRIOR, T. I. Stereochemistry and drug efficacy and development: relevance of chirality to antidepressant and antipsychotic drugs. *Ann. Med.* **2002**, *34*, 537-543.

30. DE MAGALHÃES PINTO, M. M.; TIRITAN, M. E.; GARCIA FERNANDES, C. F.; CASS, Q. B. Fases estacionárias quirais baseadas en derivados xantónicos (Chiral stationary phases besed on xanthone derivatives). WO 2011010284, January 27, 2011[cit. 2011-03-29]. Dostupné z URL:
http://v3.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=2011010284A2&KC=A2&FT=D&date=20110127&DB=EPODOC&locale=en_EP